

(19) World Intellectual Property Organization  
International Bureau(43) International Publication Date  
27 June 2002 (27.06.2002)

PCT

(10) International Publication Number  
**WO 02/50091 A1**(51) International Patent Classification<sup>7</sup>: **C07H 17/08**,  
A61K 31/70

(21) International Application Number: PCT/GB01/05665

(22) International Filing Date:  
20 December 2001 (20.12.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
0031309.8 21 December 2000 (21.12.2000) GB  
0126277.3 1 November 2001 (01.11.2001) GB  
0126276.5 1 November 2001 (01.11.2001) GB(71) Applicant (for all designated States except US): **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

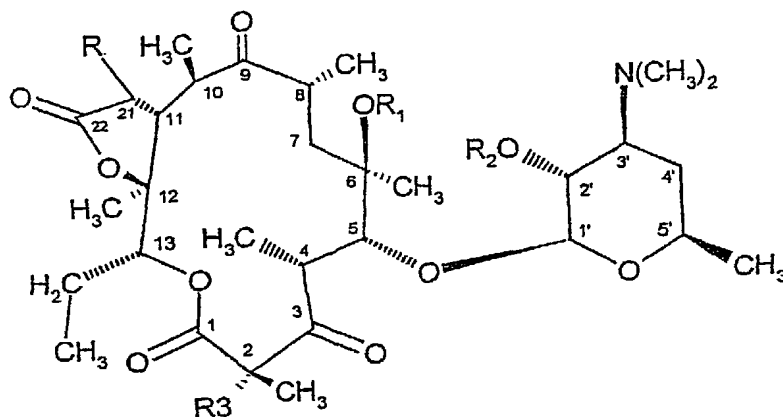
(72) Inventors; and

(75) Inventors/Applicants (for US only): **ANDREOTTI, Daniele** [IT/IT]; GlaxoSmithKline SpA, Via Alessandro Fleming, 2, I-37100 Verona (IT). **ARISTA, Luca** [IT/IT]; GlaxoSmithKline SpA, Via Alessandro Fleming, 2, I-37100 Verona (IT). **BIONDI, Stefano** [IT/IT]; GlaxoSmithKline SpA, Via Alessandro Fleming, 2, I-37100 Verona (IT). **CARDULLO, Francesca** [IT/IT]; GlaxoSmithKline SpA, Via Alessandro Fleming, 2, I-37100Verona (IT). **DAMIANI, Frederica** [IT/IT]; GlaxoSmithKline SpA, Via Alessandro Fleming, 2, I-37100 Verona (IT). **LOCIURO, Sergio** [IT/IT]; GlaxoSmithKline SpA, Via Alessandro Fleming, 2, I-37100 Verona (IT). **MARCHIORO, Carla** [IT/IT]; GlaxoSmithKline SpA, Via Alessandro Fleming, 2, I-37100 Verona (IT). **MERLO, Giancarlo** [IT/IT]; GlaxoSmithKline SpA, Via Alessandro Fleming, 2, I-37100 Verona (IT). **MINGARDI, Anna** [IT/IT]; GlaxoSmithKline SpA, Via Alessandro Fleming, 2, I-37100 Verona (IT). **NICCOLAI, Daniela** [IT/IT]; GlaxoSmithKline SpA, Via Alessandro Fleming, 2, I-37100 Verona (IT). **PAIO, Alfredo** [IT/IT]; GlaxoSmithKline SpA, Via Alessandro Fleming, 2, I-37100 Verona (IT). **PIGA, Elisabetta** [IT/IT]; GlaxoSmithKline SpA, Via Alessandro Fleming, 2, I-37100 Verona (IT). **POZZAN, Alfonso** [IT/IT]; GlaxoSmithKline SpA, Via Alessandro Fleming, 2, I-37100 Verona (IT). **SERI, Catia** [IT/IT]; GlaxoSmithKline SpA, Via Alessandro Fleming, 2, I-37100 Verona (IT). **TARSI, Luca** [IT/IT]; GlaxoSmithKline SpA, Via Alessandro Fleming, 2, I-37100 Verona (IT). **TERRENI, Silvia** [IT/IT]; GlaxoSmithKline SpA, Via Alessandro Fleming, 2, I-37100 Verona (IT). **TIBASCO, Jessica** [IT/IT]; GlaxoSmithKline SpA, Via Alessandro Fleming, 2, I-37100 Verona (IT).(74) Agents: **DOLTON, Peter, I.** et al.; GlaxoSmithKline, Corporate Intellectual Property (CN9.25.1), 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,

[Continued on next page]

(54) Title: MACROLIDE ANTIBIOTICS

(57) Abstract: The present invention relates to 11,12  $\gamma$  lactone ketolides of formula (I) wherein R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> are as defined herein and pharmaceutically acceptable salts and solvates thereof, to process for their preparation and their use in therapy or prophylaxis of systemic or topical bacterial infections in a human or animal body.



CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**

— with international search report

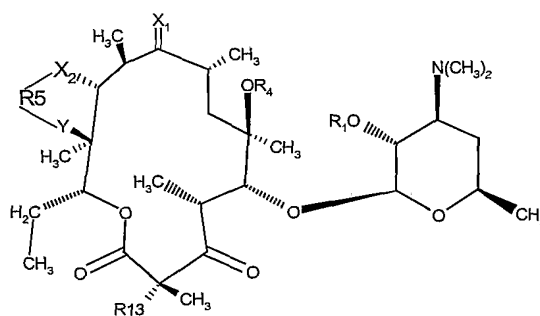
**(84) Designated States (regional):** ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

## MACROLIDE ANTIBIOTICS

The present invention relates to novel semi-synthetic macrolides having antibacterial activity. More particularly this invention relates to 11,12  $\gamma$  lactone ketolides, to processes for their preparation, to compositions containing them and to their use in medicine.

EP 1114826 inter alia generically discloses macrolide compounds of formula (A) having antibacterial activity

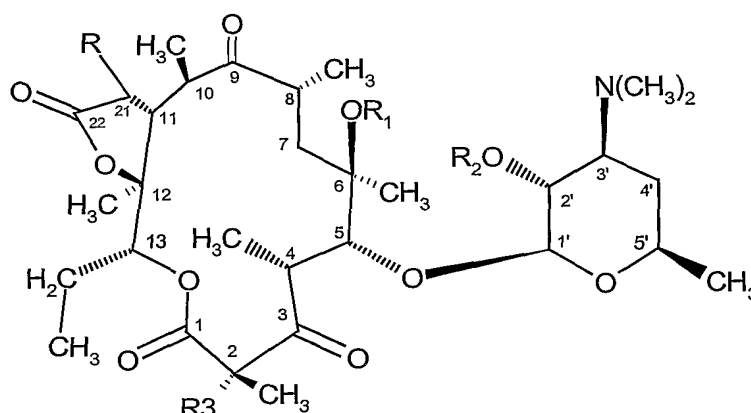


(A)

wherein  $R_1$  is hydrogen or a hydroxyl protecting group;  $R_4$  is inter alia an optionally substituted  $C_{1-10}$  alkyl,  $X_1$  is inter alia oxygen,  $X_2$  is inter alia  $CH_2$ ,  $Y$  is NH, O or S,  $R_5$  is inter alia  $C(O)$  and  $R_{13}$  is hydrogen or halo.

We have now found novel 11,12  $\gamma$  lactone ketolides having antibacterial activity.

Thus, the present invention provides compounds of general formula (I)



(I)

wherein

$R$  is hydrogen, cyano,  $(CH_2)_nA-X-R_4$  or  $(CH_2)_nR_5$ ;

$A$  is a group selected from  $-N(R_6)-$ ,  $-N[C(O)R_6]-$ ,  $-N(R_6)C(O)-$ ,  $-N(R_6)S(O)_2-$ ,  $-N(R_6)C(O)O-$ ,  $-N=C(R_6)-$  or  $-N(R_6)C(Y)N(R_7)-$ ;

R<sub>1</sub> is C<sub>1-6</sub> alkyl or C<sub>3-6</sub> alkenyl;

R<sub>2</sub> is hydrogen or a hydroxyl protecting group;

R<sub>3</sub> is hydrogen or halogen;

X is a bond, a C<sub>1-10</sub> alkylene, a C<sub>2-10</sub> alkenylene or a C<sub>2-10</sub> alkynylene chain wherein said chains are:

i) optionally interrupted by a bivalent radical group selected from -O-, -N(R<sub>8</sub>)-, -C(O)-, -N(R<sub>8</sub>)C(Y)N(R<sub>9</sub>)-, -S(O)m-, -N(R<sub>8</sub>)C(O)-, -C(O)N(R<sub>8</sub>)-, -N(R<sub>8</sub>)C(O)C(O)-, -C(O)O- or -C(NOR<sub>6</sub>)- and/or

ii) optionally substituted by one or two groups selected from:

C<sub>1-4</sub> alkyl, oxo, C<sub>1-4</sub> alkoxy, halogen, cyano, phenoxy, hydroxy, NR<sub>8</sub>R<sub>9</sub>, N(R<sub>8</sub>)C(O)R<sub>9</sub>, =NOR<sub>6</sub>, NR<sub>8</sub>C(Y)NR<sub>9</sub> or optionally substituted phenyl;

R<sub>4</sub> is selected from:

hydrogen,

optionally substituted phenyl,

optionally substituted C<sub>3-7</sub> cycloalkyl,

optionally substituted 9 to 10 membered fused bicyclic carbocyclic,

optionally substituted 5 or 6 membered heteroaryl in which the 5-membered heteroaryl contains at least one heteroatom selected from oxygen, sulphur or nitrogen and the 6-membered heteroaryl group contains from 1 to 3 nitrogen atoms,

optionally substituted 5-6 membered heterocyclic,

or

R<sub>4</sub> is an optionally substituted 9 or 10 membered fused bicyclic heterocyclic having at least one heteroatom selected from oxygen, sulphur or nitrogen;

R<sub>5</sub> is a 5 or 6 membered heterocyclic containing at least one nitrogen, optionally substituted

by one or two groups selected from oxo or 9 or 10 membered fused bicyclic heterocyclic having at least one heteroatom selected from oxygen, sulphur or nitrogen;

R<sub>6</sub> and R<sub>7</sub> are independently hydrogen, C<sub>1-4</sub> alkyl or phenyl which is optionally substituted by one or two C<sub>1-4</sub> alkyl groups;

R<sub>8</sub> and R<sub>9</sub> are independently hydrogen, phenyl (which may be substituted by one or two C<sub>1-4</sub> alkyl) or R<sub>8</sub> and R<sub>9</sub> are independently C<sub>1-4</sub> alkyl which is optionally substituted by 1 or 2 groups selected from:

phenyl, C<sub>1-4</sub> alkoxy,

cyano,

5-membered heteroaryl containing 1 or 2 heteroatoms selected from oxygen, sulphur or nitrogen or the 6-membered heteroaryl group contains from 1 to 3 nitrogen atoms,

hydroxy,

oxo,

carboxy;

Y is an oxygen or a sulphur atom;

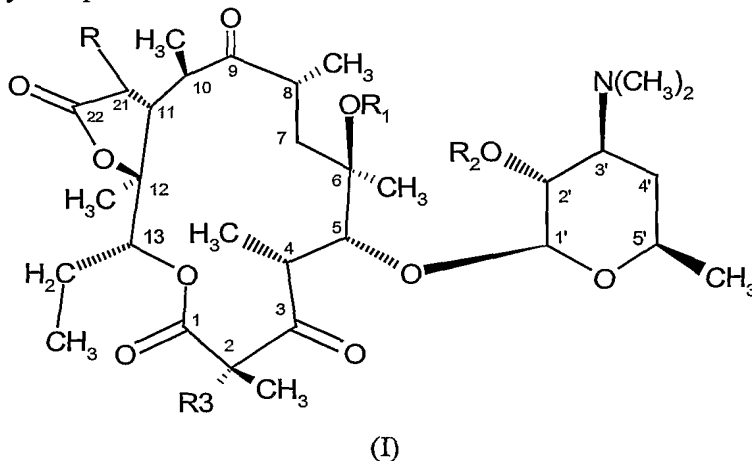
n is 0 or an integer from 1 to 3;

m is 0, 1 or 2;

and pharmaceutically acceptable salts and solvates thereof.



A further embodiment of the invention provides compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof,



5

wherein

R is (CH<sub>2</sub>)<sub>n</sub>A-X-R<sub>4</sub>;

A is a group selected from -N(R<sub>5</sub>)-, -N(R<sub>5</sub>)C(O)-, -N(R<sub>5</sub>)S(O)<sub>2</sub>-, or -N(R<sub>5</sub>)C(Y)N(R<sub>6</sub>)-;

R<sub>1</sub> is hydrogen, C<sub>1-6</sub> alkyl or C<sub>3-6</sub> alkenyl;

10 R<sub>2</sub> is hydrogen or a hydroxyl protecting group;

R<sub>3</sub> is hydrogen or halogen;

X is optionally substituted C<sub>1-10</sub> alkylene chain interrupted by a bivalent radical group selected from -O-, -N(R<sub>5</sub>)-, -C(O)-, -N(R<sub>5</sub>)C(Y)N(R<sub>6</sub>)-, -S(O)<sub>m</sub>-, -N(R<sub>5</sub>)C(O)-, -C(O)N(R<sub>5</sub>)-, -N(R<sub>5</sub>)C(O)C(O)-, -C(O)O- or -C(NOR<sub>7</sub>)- or

15 X is optionally substituted C<sub>2-10</sub> alkenylene or optionally substituted C<sub>2-10</sub> alkynylene chain wherein said C<sub>2-10</sub> alkenylene or C<sub>2-10</sub> alkynylene chains are optionally interrupted by a bivalent radical group selected from -O-, -N(R<sub>5</sub>)-, -C(O)-, -N(R<sub>5</sub>)C(Y)N(R<sub>6</sub>)-, -S(O)<sub>m</sub>-, -N(R<sub>5</sub>)C(O)-, -C(O)N(R<sub>5</sub>)-, -N(R<sub>5</sub>)C(O)C(O)-, -C(O)O- or -C(NOR<sub>7</sub>)-;

R<sub>4</sub> is selected from:

20 hydrogen;

optionally substituted phenyl;

optionally substituted C<sub>3-7</sub> cycloalkyl;

optionally substituted 9 to 10 membered aromatic fused bicyclic carbocyclic ring;

25 optionally substituted 5 or 6 membered heteroaryl in which the 5-membered heteroaryl contains at least one heteroatom selected from oxygen, sulphur or nitrogen and the 6-membered heteroaryl group contains from 1 to 3 nitrogen atoms;

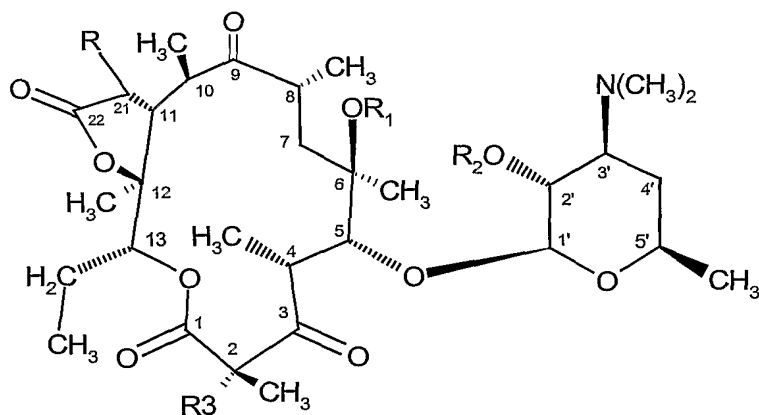
optionally substituted 5-6 membered heterocyclic,

or

30 R<sub>4</sub> is optionally substituted fused bicyclic heteroaryl groups containing 9 or 10 ring members having at least one heteroatom selected from oxygen, sulphur or nitrogen;

R<sub>5</sub> and R<sub>6</sub> are independently hydrogen, phenyl (which may be substituted by one or two C<sub>1-4</sub> alkyl) or a nitrogen protecting group or R<sub>5</sub> and R<sub>6</sub> are independently C<sub>1-4</sub> alkyl which is optionally substituted by 1 or 2 groups selected from:

- phenyl, C<sub>1-4</sub> alkoxy,  
 C<sub>1-4</sub> alkyl,  
 cyano,  
 nitro,
- 5 5-membered heteroaryl containing 1 or 2 heteroatoms selected from oxygen, sulphur or nitrogen and the 6-membered heteroaryl group contains from 1 to 3 nitrogen atoms;  
 hydroxy,  
 oxo,  
 carboxy;
- 10 R<sub>7</sub> is hydrogen, C<sub>1-4</sub> alkyl or phenyl;  
 Y is an oxygen or a sulphur atom;  
 n is 0 or an integer from 1 to 5;  
 m is 0, 1 or 2;
- 15 Yet a further embodiment of the invention provides compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof,



(I)

- 20 wherein
- R is hydrogen, cyano or (CH<sub>2</sub>)<sub>n</sub>A(CH<sub>2</sub>)<sub>m</sub>R<sub>4</sub>;
- R<sub>1</sub> is C<sub>1-6</sub> alkyl or C<sub>3-6</sub> alkenyl;
- R<sub>2</sub> is hydrogen or a hydroxyl protecting group;
- 25 R<sub>3</sub> is hydrogen or halogen;
- R<sub>4</sub> is selected from:
- hydrogen;
- optionally substituted phenyl;
- optionally substituted 9 to 10 membered aromatic fused bicyclic carbocyclic
- 30 ring;
- optionally substituted 5 or 6 membered heteroaryl in which the 5-membered heteroaryl contains at least one heteroatom selected from oxygen, sulphur or

nitrogen and the 6-membered heteroaryl group contains from 1 to 3 nitrogen atoms; or

R<sub>4</sub> is optionally substituted fused bicyclic heteroaryl groups containing 9 or 10 ring members having at least one heteroatom selected from oxygen, sulphur or nitrogen;

A is a bond or a group selected from N(R<sub>5</sub>), N[C(O)R<sub>5</sub>], N(R<sub>5</sub>)C(O), N(R<sub>5</sub>)S(O<sub>2</sub>), N(R<sub>5</sub>)C(O)O, N=C(R<sub>6</sub>) or N(R<sub>5</sub>)C(X)N(R<sub>6</sub>);

R<sub>5</sub> and R<sub>6</sub> are independently hydrogen, phenyl, or C<sub>1-4</sub> alkyl;

X is an oxygen or a sulphur atom;

n or m are independently 0 or an integer from 1 to 5 with the proviso that the sum of n and m is 0 or an integer from 1 to 5;  
and pharmaceutically acceptable salts and solvates thereof.

Suitable pharmaceutically acceptable salts of the compounds of general formula (I) include acid addition salts formed with pharmaceutically acceptable organic or inorganic acids, for example hydrochlorides, hydrobromides, sulphates, alkyl- or arylsulphonates (e.g. methanesulphonates or p-toluenesulphonates), phosphates, acetates, citrates, succinates, tartrates, fumarates and maleates.

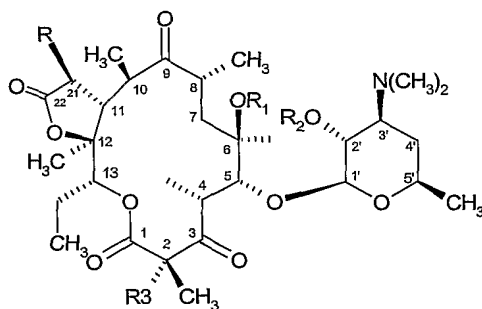
The compound of formula (I) and salts thereof may form solvates and the invention includes all such solvates. The solvates may, for example, be hydrates.

References hereinafter to a compound according to the invention include both compounds of formula (I) and their pharmaceutically acceptable acid addition salts together with pharmaceutically acceptable solvates.

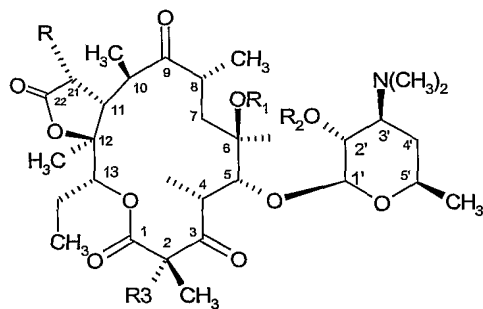
In the general formula (I) as drawn, the solid wedge shaped bond indicates that the bond is above the plane of the paper. The broken bond indicates that the bond is below the plane of the paper.

It will be appreciated by those skilled in the art that the compounds of formula (I) when R is not hydrogen contain at least one chiral centre (namely the carbon atom shown as 21 in formula (I)) and this may be represented by the formulae (1a) and (1b).

The configuration for the carbon atom shown as 21 in formula 1a is hereinafter referred to as the β configuration and in formula 1b as the 21α configuration.



1a



1b

- 5 It is to be understood that the two diastereoisomers (1a, 1b) and mixtures thereof are encompassed within the scope of the present invention.

Compounds wherein  $R_2$  represents a hydroxyl protecting group are in general intermediates for the preparation of other compounds of formula (I).

10

When the group  $OR_2$  is a protected hydroxyl group this is a non-toxic protecting group, conveniently  $OR_2$  is an acyloxy group (i.e. acetoxy or benzyloxy).

- 15 The term  $C_{1-4}$  alkyl as used herein as a group or a part of the group refers to a straight or branched alkyl group containing from 1 to 4 carbon atoms; examples of such groups include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl and tert-butyl.

- 20 The term  $C_{1-10}$  alkylene chain refers to straight or branched chain containing from 1 to 10 carbon atoms examples of such group include, but are not limited to methylene, ethylene, propylene, isopropylene, n-butylene, isobutylene, tert-butylene, pentylene, n-heptylene, n-octylene, n-nonylene and n-decylene.

- 25 The term  $C_{2-10}$  alkenylene chain refers to a straight or branched alkylene chain containing from 2 to 12 carbon atoms and having at least one double bond; examples of such groups include ethylene, 2-propenylene, 1-propenylene, isopropenylene, 2-butenylene, 2-pentenylene, 2-hexenylene and the like.

- 30 The term  $C_{2-10}$  alkynylene chain refers to a straight or branched alkylene chain containing from 2 to 12 carbon atoms and having at least one triple bond; examples of such groups include ethynylene, 2-propynylene, 1-propynylene, isopropynylene, 2-butylnylene, 2-pentylnylene, 2-hexenylene and the like.

The term halogen refers to a fluorine, chlorine, bromine or iodine atom.

When R<sub>4</sub> is a 5 or 6 membered heteroaryl group according to the invention this includes furanyl, thiophenyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,3-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-triazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-oxadiazolyl, 1,2,5-thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,4 oxadiazolyl, 1,2,5-triazinyl or 1,3,5-triazinyl and the like.

The term 9 to 10 membered fused bicyclic heterocyclic group refers to a 5,6/6,5 or 6,6 bicyclic ring system, containing at least one heteroatom selected from oxygen, sulphur or nitrogen, which may be saturated, unsaturated or aromatic. The term 9 to 10 membered fused bicyclic heterocyclic group also refers to a phenyl fused to one 5 or 6 membered heterocyclic group. Example of such groups include benzofuranyl, benzothiophenyl, indolyl, benzoxazolyl, 3H-imidazo[4,5-c]pyridin-yl, dihydrophthaziny, 1H-imidazo[4,5-c]pyridin-1-yl, imidazo[4,5-b]pyridyl, 1,3 benzo[1,3]dioxolyl, 2H-chromanyl, isochromanyl, 5-oxo-2,3 dihydro-5H-[1,3]thiazolo[3,2-a]pyrimidinyl, 1,3-benzothiazolyl, 1,4,5,6 tetrahydropyridazyl, 1,2,3,4,7,8 hexahydropteridinyl, 2-thioxo-2,3,6,9-tetrahydro-1H-purin-8-yl, 3,7-dihydro-1H-purin-8-yl, 3,4 dihydropyrimidin-1-yl, 2,3 -dihydro-1,4-benzodioxinyl, benzo[1,3]dioxolyl, 2H-chromenyl, chromanyl, 3,4-dihydrophthalazinyl, 2,3 dihydro-1H-indolyl, 1,3-dihydro-2H-isoindol-2-yl, 2,4,7-trioxo-1,2,3,4,7,8-hexahydropteridinyl, thieno[3,2-d]pyrimidinyl, 4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidinyl, 1,3 dimethyl-6-oxo-2-thioxo-2,3,6,9-tetrahydro-1H-purinyl, 1,2 dihydroisoquinolinyl, 2-oxo-1,3-benzoxazolyl, 2,3-dihydro-5H-1,3-thiazolo[3,2-a]pyrimidinyl, 5,6,7,8-tetrahydro-quinazolinyl, 4-oxochromanyl, 1,3-benzothiazolyl, benzimidazolyl, benzotriazolyl, purinyl, furylpyridyl, thiophenylpyrimidinyl, thiophenylpyridyl, pyrrolylpyridyl, oxazolylpyridyl, thiazolylpyridyl, 3,4 dihydropyrimidin-1-yl imidazolylpyridyl, quinolyl, isoquinolinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pyrazolyl[3,4]pyridine, 1,2 dihydroisoquinolinyl, cinnolinyl, 2,3dihydro-benzo[1,4]dioxin-6-yl, 4,5,6,7-tetrahydro-benzo[b]thiophenyl-2-yl, 1,8naphthyridinyl, 1,6naphthyridinyl, 3,4 dihydro-2H-1,4-benzothiazine, 4,8-Dihydroxy-quinolinyl, 1-oxo-1,2-dihydro-isoquinolinyl or 4-phenyl-[1,2,3]thiadiazolyl and the like.

The term 5 or 6 membered heterocyclic group refers to 5 or 6 ring member containig at least one heteroatom selected from oxygen, sulphur or nitrogen, which may be saturated, unsaturated. Examples of such groups include piperidyl, 2-oxodihydrofuranyl, piperazinyl, morpholinyl, pyrazolidinyl, 1,2 dihydro-3H-pyrazolyl, imidazolidinyl or pyrrolidinyl and the like.

The term 9 to 10 membered fused bicyclic carbocyclic group refers to a 5,6/6,5 or 6,6 bicyclic carbocyclic ring system which may be saturated, unsaturated or aromatic. It also refers to a phenyl fused to one 5 or 6 membered saturated or unsaturated carbocyclic group. Examples of such groups include naphthyl, 1, 2, 3, 4 tetrahydronaphthyl, indenyl or indanyl and the like.

The term optionally substituted phenyl, optionally substituted 5-6 membered heterocyclic group, optionally substituted 9 to 10 membered fused bicyclic carbocyclic group, optionally

substituted 9 to 10 membered fused bicyclic heterocyclic group or optionally substituted 5 or 6 membered heteroaryl group this refers to a 5-6 membered heterocyclic, a 9 to 10 membered fused bicyclic carbocyclic, a 9 to 10 fused bicyclic heterocyclic or 5 or 6 membered heteroaryl as defined above which is substituted by 1 to 4 groups, which may be the same or different, selected from (CH<sub>2</sub>)<sub>p</sub>R<sub>10</sub> group wherein p is zero or an integer from 1 to 4 and R<sub>10</sub> is selected from:

- halogen,
- C<sub>1-4</sub>alkoxy,
- C<sub>1-4</sub>alkyl,
- hydroxy,
- cyano,
- nitro,
- oxo,
- trifluoromethyl,
- carboxy,
- NR<sub>8</sub>R<sub>9</sub>,
- COR<sub>8</sub>,
- CONR<sub>8</sub>R<sub>9</sub>,
- NHCOR<sub>8</sub>,
- NHSO<sub>2</sub>R<sub>8</sub>,
- S(O)<sub>q</sub>R<sub>6</sub> (wherein q is 0 or an integer from 1 to 2),
- phenyl (optionally substituted by halogen, C<sub>1-4</sub>alkoxy or NR<sub>8</sub>R<sub>9</sub>);
- phenoxy;
- 5-membered heteroaryl containing at least 1 heteroatoms selected from oxygen, sulphur or nitrogen and a 6-membered heteroaryl group containing at least 1 nitrogen atom which 5-6membered heteroaryl may be substituted by C<sub>1-4</sub>alkyl or cyano.
- or
- 9 or 10 membered fused bicyclic heterocyclic .

- When R<sub>4</sub> is an optionally substituted C<sub>3-7</sub> cycloalkyl, such a group is optionally substituted by 1 or 2 substituents which may be the same or different and selected from C<sub>1-4</sub> alkyl, halogen, cyano, nitro, trifluoromethyl and NR<sub>6</sub>R<sub>7</sub>.

- When X is a C<sub>1-10</sub> alkylene, a C<sub>2-10</sub> alkynylene or a C<sub>2-10</sub> alkenylene chain which is interrupted by a bivalent radical group selected from -O-, -NR<sub>8</sub>-, -C(O)-, -N(R<sub>8</sub>)C(Y)N(R<sub>9</sub>)-, -S(O)m-, -N(R<sub>8</sub>)C(O)-, -C(O)N(R<sub>8</sub>)-, N(R<sub>8</sub>)C(O)C(O)-, -C(O)O- or -C(NOR<sub>6</sub>)-, this refers for example to C<sub>1-10</sub> alkylene-O-, C<sub>1-10</sub>alkylene-NR<sub>8</sub>C(Y)NR<sub>9</sub>-, C<sub>1-10</sub>alkylene-NR<sub>8</sub>-, C<sub>1-10</sub> alkylene-C(O)-, C<sub>1-10</sub>alkylene-S(O)m-, C<sub>1-10</sub> alkylene-NR<sub>8</sub>C(O)-, C<sub>1-10</sub> alkylene-C(O)NR<sub>8</sub>-, C<sub>1-10</sub> alkylene-N(R<sub>8</sub>)C(O)C(O)-, C<sub>1-10</sub> alkylene-C(O)O-, C<sub>1-10</sub> alkylene C(NOR<sub>6</sub>), C<sub>2-10</sub>alkenylene-O-, C<sub>2-10</sub>alkenylene-NR<sub>8</sub>-, C<sub>2-10</sub>alkenylene-C(O)-, C<sub>2-10</sub>alkenylene-NR<sub>8</sub>C(Y)NR<sub>9</sub>-, C<sub>2-10</sub> alkenylene-S(O)m-, C<sub>2-10</sub> alkenylene-NR<sub>8</sub>C(O)-, C<sub>2-10</sub> alkenylene-C(O)NR<sub>8</sub>-, C<sub>2-10</sub> alkenylene-N(R<sub>8</sub>)C(O)C(O)-, C<sub>2-10</sub> alkenylene-C(O)O-, C<sub>2-10</sub> alkenylene-C(NOR<sub>6</sub>), C<sub>2-10</sub>alkynylene-O-, C<sub>2-10</sub>alkynylene-NR<sub>8</sub>-, C<sub>2-</sub>

$_{10}$ alkynylene-C(O)-,  $C_{2-10}$ alkynylene-NR<sub>8</sub>C(Y)NR<sub>9</sub>-,  $C_{2-10}$ alkynylene-S(O)m-,  $C_{2-10}$ alkynylene-NR<sub>8</sub>C(O)-,  $C_{2-10}$ alkynylene-C(O)NR<sub>8</sub>-,  $C_{2-10}$ alkynylene-N(R<sub>8</sub>)C(O)C(O)-,  $C_{2-10}$ alkynylene-C(O)O-,  $C_{2-10}$ alkynylene-C(NOR<sub>6</sub>),

or this refers to a  $C_{1-10}$  alkylene, a  $C_{2-10}$  alkenylene or a  $C_{2-10}$  alkynylene chain containing a bivalent radical group selected from:  
-O-, -NR<sub>8</sub>-, -C(O)-, -NR<sub>8</sub>C(Y)NR<sub>9</sub>-, -S(O)m-, -NR<sub>8</sub>C(O)-, -C(O)NR<sub>8</sub>-.

When A is -N(R<sub>6</sub>)-, -N(R<sub>6</sub>)S(O)<sub>2</sub>- or -N(R<sub>6</sub>)C(Y)N(R<sub>7</sub>) and when X is an optionally substituted  $C_{1-10}$  alkylene interrupted by a bivalent radical selected from -O-, -N(R<sub>8</sub>)-, -N(R<sub>8</sub>)C(Y)N(R<sub>9</sub>)-, -S(O)m-, -N(R<sub>8</sub>)C(O)- or -N(R<sub>8</sub>)C(O)C(O)- said bivalent radicals are preferably linked to A group by an optionally substituted alkylene chain containing at least two carbon atoms.

When A is -N(R<sub>6</sub>)-, -N(R<sub>6</sub>)S(O)<sub>2</sub>- or -N(R<sub>5</sub>)C(Y)N(R<sub>7</sub>) and when X is an optionally substituted  $C_{2-10}$  alkenylene or an optionally substituted  $C_{2-10}$  alkynylene chain and when these chains are interrupted by a bivalent radical selected from -O-, -N(R<sub>8</sub>)-, -N(R<sub>8</sub>)C(Y)N(R<sub>9</sub>)-, -S(O)m-, -N(R<sub>8</sub>)C(O)- or -N(R<sub>8</sub>)C(O)C(O)- said bivalent radicals are preferably linked to the A group by an optionally substituted alkenylene or alkynylene chain containing at least 4 carbon atoms and having -CH<sub>2</sub>- as terminal groups.

A preferred group of compounds of formula (I) are those in which the carbon atom shown as 21 is in the  $\beta$  configuration.

R is preferably (CH<sub>2</sub>)<sub>n</sub>A-X-R<sub>4</sub> or (CH<sub>2</sub>)<sub>n</sub>R<sub>5</sub>.

R<sub>1</sub> is preferably methyl or 2-propenyl.

R<sub>2</sub> is preferably hydrogen.

R<sub>3</sub> is preferably hydrogen or fluorine.

When R<sub>4</sub> is a 5 or 6 membered heteroaryl group this is preferably imidazolyl, imidazolyl, pyrazolyl, thiophenyl, 1,2,3-triazolyl, pyridinyl or furanyl.

When R<sub>4</sub> or R<sub>5</sub> is a 5 or 6 membered heterocyclic group this is preferably imidazolidinyl or pyrrolidinyl.

When R<sub>4</sub> is a 9 or 10 membered fused bicyclic heteroaryl group this is preferably quinolinyl, quinoxalinyl, indolyl, purinyl, 1,3 benzo[1,3]dioxolyl, benzothiazolyl, 1H-benzimidazol-yl, 1,3-benzoxazolyl, 1H-pyrrolo[2,3-b]pyridinyl, 1,3-dihydro-2H-isoindolyl, 3H-imidazo[4,5-c]pyridin-3-yl, 3H-imidazo[4,5-b]pyridin-3-yl, 7H-purin-7-yl, 1H-imidazo[4,5-c]pyridin-1-yl, 4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl.

R<sub>5</sub> is preferably 1-pyrrolidinyl which is optionally substituted by one oxo or benzo[1,3]dioxolyl.

X is preferably a C<sub>1-5</sub> alkylene, a C<sub>2-5</sub> alkenylene or a C<sub>2-5</sub> alkynylene chain wherein said chains are:

- i) optionally interrupted by a bivalent radical group selected from -O-, -N(R<sub>8</sub>)-, -C(O)-, -N(R<sub>8</sub>)C(Y)N(R<sub>9</sub>)-, -S(O)m-, -N(R<sub>8</sub>)C(O)-, -C(O)N(R<sub>8</sub>)-, -N(R<sub>8</sub>)C(O)C(O)-, -C(O)O- or -C(NOR<sub>6</sub>)-and/or
  - ii) optionally substituted by one or two groups selected from:
- 10 C<sub>1-4</sub> alkyl, oxo, C<sub>1-4</sub> alkoxy, halogen, cyano, phenoxy, hydroxy, NR<sub>8</sub>R<sub>9</sub>, N(R<sub>8</sub>)C(O)R<sub>9</sub>, =NOR<sub>6</sub>, NR<sub>8</sub>C(Y)NR<sub>9</sub> or optionally substituted phenyl.

n is preferably 0 or 1.

- 15 Preferred compounds of the invention are those wherein A is selected from -NH-, -NHC(O)- or -NHC(Y)NH-. Within this class the compounds in which n is 0 or 1 are particular preferred.

- 20 A preferred class of compounds of formula (I) are those wherein X is a C<sub>1-4</sub> alkylene chain which is optionally interrupted by a bivalent radical selected from -O-, -NH-, -C(O)-, -NHC(O)-, -S(O)2-, -S- and /or such a C<sub>1-4</sub> alkylene chain is optionally substituted by one group selected from NH<sub>2</sub>, C<sub>1-4</sub> alkyl, oxo or N-OH.

- 25 A particularly preferred group of compounds of formula (I) is that wherein R<sub>4</sub> is phenyl (optionally substituted by 1 to 3 groups which may be the same or different selected from nitro, amino, methyl, C<sub>1-4</sub> alkoxy ie methoxy or hydroxy), 1-imidazolyl (optionally substituted by 1 to 3 groups which may be the same or different selected from pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, phenyl, m-nitrophenyl, dichlorophenyl, C<sub>1-4</sub> alkyl i.e methyl, trifluoromethylphenyl, thiophen-2-yl, thiazol-2-yl), 3-trifluoromethylpyrazol-4-yl, 1-pyrazolyl (optionally substituted by 1 to 3 groups which may be the same or different selected from alogen (i.e. chlorine, fluorine), pyridin-2-yl, pyridin-4-yl, quinolin-2-yl, quinolin-4-yl, quinoxalin-2-yl, pyrimidin-4-yl, C<sub>1-4</sub> alkyl i.e methyl, 1,3 benzooxazol-2-yl, p-chloro phenyl, difluoro phenyl, pyrazin-2-yl thiazol-5-yl, 1H-indol-3-yl, 1H-indol-2-yl, 3-methoxy-quinoxalin-2-yl, 2-quinolinyl 3-quinolinyl, 4-quinolinyl, 4-pyridinyl, 3-pyridinyl (optionally substituted by one amino), 5methyl furan-2-yl, 3-thiophenyl, 6-methoxy-7H-purin-7-yl, 35 quinoxalin-2-yl, 3-methoxy quinoxalin-2-yl 6-methoxy-2-oxo1, 3-benzoxazol-3(2H)-yl, 1H-pyrrolo[2,3-b]pyridin-1-yl, 2-(methylthio)-1H-benzimidazol-1-yl, 1,3-dioxo-1,3-dihydro-2H-isindol-2-yl, 6-methoxy-2-oxo-1,3-benzoxazol-3(2H)-yl, 3H-imidazo[4,5-b]pyridin-3-yl, 1,3-benzoxazol-2-yl, benzothiazol-2-yl, 1,3 benzo[1,3]dioxolyl, 3-(5-cyano-3,4-dimethylthien-2-yl)-1H-1,2,4-triazol-1-yl, 2,3-dihydro-benzo[1,4]dioxin-6-yl, 2,4-dimethyl-40 1,3-thiazol-5-yl or 4-oxo-4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl.



A particularly preferred group of compounds of formula (I) are those wherein R<sub>1</sub> is methyl, R<sub>2</sub> or R<sub>3</sub> is hydrogen, A is -NH-, -NHC(O)-, X is C<sub>1-4</sub> alkylene chain which is optionally interrupted by a bivalent radical selected from -O-, -NH-, -C(O)-, -NHC(O)-, -S(O)<sub>2</sub>- -S- and /or such a C<sub>1-4</sub> alkylene chain is optionally substituted by one group selected from NH<sub>2</sub>, C<sub>1-4</sub> alkyl, oxo or N-OH, R<sub>4</sub> is a group selected from 4-(pyridin-3-yl)-imidazol-1-yl, 4-(pyridin-3-yl)-imidazol-1-yl, quinoxalin-2-yl, quinoxalin-2-yl, quinolin-4-yl, quinoxalin-2-yl, -(2,3-dihydro-benzo[1,4]dioxin-6-yl, 4-oxo-4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl, 4-methoxy-3-nitro-phenyl, 2-hydroxy-4,5-dimethoxy-phenyl, 3-hydroxy-4-methoxy-phenyl, 3,4-dimethoxy-phenyl, 4-hydroxy-3-methoxy-phenyl, 3-methoxy-quinoxalin-2-yl, 3-amino-4-methoxy-phenyl, 4-(pyridin-3-yl)-imidazol-1-yl, quinolin-4-yl, 4-pyrimidin-4-yl-pyrazol-1-yl, 2-(methylthio)-1H-benzimidazol-1-yl, -[3-(4-chlorophenyl)-1H-pyrazol-5-yl]propylamino)-methylene], 6-methoxy-2-oxo-1,3-benzoxazol-3(2H)-yl, 1H-pyrrolo[2,3-b]pyridin-1-yl, 3-(2,4-dimethyl-1,3-thiazol-5-yl)-1H-pyrazol-1-yl, 4-phenyl-1H-imidazol-1-yl, 4-pyridin-4-yl-1H-imidazol-1-yl, thiophen-2-yl, 3-(5-cyano-3,4-dimethylthien-2-yl)-1H-1,2,4-triazol-1-yl, quinolin-3-yl, 1,3-thiazol-2-yl and n is 0 or 1.

Particularly preferred compounds of the invention are selected from:

- (11S, 21R)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(4-(pyridin-3-yl)-imidazol-1-yl)-butyramidomethyl)-methylene]-erythromycin A;
- (11S, 21R)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(4-(pyridin-3-yl)-imidazol-1-yl)-propionamidomethyl)-methylene]-erythromycin A;
- (11S,21R)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(quinoxalin-2-ylsulfanyl)-acetamidomethyl)-methylene]-erythromycin A;
- (11S,21R)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(quinoxalin-2-ylsulfanyl)-propionamidomethyl)-methylene]-erythromycin A;
- (11S,21R)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-[(quinolin-4-ylmethyl)-amino]-methyl)-methylene]-erythromycin A;
- (11S, 21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(quinolin-4-yl)-propionamido)-methylene]-erythromycin A;
- (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(quinoxalin-2-ylsulfanyl)-acetamido)-methylene]-erythromycin A;
- (11S, 21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-4-oxo)-butyramido)-methylene]-erythromycin A;
- (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(4-oxo-4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl)-4-oxo-butylamido)-methylene]-erythromycin A;
- (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(4-methoxy-3-nitro-phenyl)-4-oxo-butylamido)-methylene]-erythromycin A;

- (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(2-hydroxy-4,5-dimethoxy-phenyl)-4-oxo-butyramido)-methylene]-erythromycin A;  
(11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(3-hydroxy-4-methoxy-phenyl)-4-oxo-butyramido)-methylene]-erythromycin A;  
5 (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(3,4-dimethoxy-phenyl)-4-oxo-butyramido)-methylene]-erythromycin A;  
(11S, 21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(4-hydroxy-3-methoxy-phenyl)-4-oxo-butyramido)-methylene]-erythromycin A;  
(11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(3-methoxy-quinoxalin-2-ylsulfanyl)-acetamido)-methylene]-erythromycin A;  
10 (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(quinoxalin-2-yloxy)-acetamido)-methylene]-erythromycin A;  
(11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(3-amino-4-methoxy-phenyl)-4-oxo-butyramide)-methylene]-erythromycin A;  
15 (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-hydroxyimino-4-(4-methoxy-3-nitro-phenyl)-butyramide)-methylene]-erythromycin A;  
(11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(quinoxaline-2-sulfonyl)-acetamide)-methylene]-erythromycin A;  
(11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(4-(pyridin-3-yl)-imidazol-1-yl)-propylamino)-methylene]-erythromycin A;  
20 (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(4-(pyridin-3-yl)-imidazol-1-yl)-ethylamino)-methylene]-erythromycin A;  
(11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(quinolin-4-yl)-butylamino)-methylene]-erythromycin A;  
25 (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(quinolin-4-yl)-ethylamino)-methylene]-erythromycin A;  
(11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(4-pyrimidin-4-yl-pyrazol-1-yl)-propylamino)-methylene]-erythromycin A;  
(11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-[2-(methylthio)-1H-benzimidazol-1-yl]propylamino)-methylene]-erythromycin A;  
30 (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-[3-(4-chlorophenyl)-1H-pyrazol-5-yl]propylamino)-methylene]-erythromycin A;  
(11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(6-methoxy-2-oxo-1,3-benzoxazol-3(2H)-yl)propylamino)-methylene]-erythromycin A;  
35 (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(1H-pyrrolo[2,3-b]pyridin-1-yl)propylamino)-methylene]-erythromycin A;

- (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-[3-(2,4-dimethyl-1,3-thiazol-5-yl)-1H-pyrazol-1-yl]propylamino)-methylene]-erythromycin A;  
 (11S, 21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(quinoxalin-2-ylsulfanyl)-propylamino)-methylene]-erythromycin A;  
 5 (11S, 21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(4-phenyl-1H-imidazol-1-yl)propyl)amino)-methylene]-erythromycin A;  
 (11S, 21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(4-pyridin-4-yl-1H-imidazol-1-yl)ethylamino)-methylene]-erythromycin A;  
 (11S, 21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-  
 10 (quinoxalin-2-ylsulfanyl)-ethylamino)-methylene]-erythromycin A;  
 (11S, 21S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(4-(thiophen-2-yl)-imidazol-1-yl)-propylamino)-methylene]-erythromycin A;  
 (11S, 21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((3-[3-(5-cyano-3,4-dimethylthien-2-yl)-1H-1,2,4-triazol-1-yl]propyl)amino)-methylene]-erythromycin  
 15 A;  
 (11S, 21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((3-quinolin-3-ylpropyl)amino)-methylene]-erythromycin A;  
 (11S, 21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((3-[4-(3-nitrophenyl)-1H-imidazol-1-yl]propyl)amino)-methylene]-erythromycin A;  
 20 (11S, 21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-[3-(1,3-thiazol-2-yl)-1H-pyrazol-1-yl]ethyl)amino)-methylene]-erythromycin A;  
 (11S, 21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-(4-phenyl-1H-imidazol-1-yl)ethyl)amino)-methylene]-erythromycin A;  
 (11S, 21R,S)-3-decladinosyl-11,12-dideoxy-2-fluoro-6-O-methyl-3-oxo-12,11-[oxycarbonyl-  
 25 (2-(quinoxalin-2-ylsulfanyl)-acetamido)-methylene]-erythromycin A;  
 (11S, 21R,S)-3-decladinosyl-11,12-dideoxy-2-fluoro-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(4-(pyridin-3-yl)-imidazol-1-yl)-propylamino)-methylene]-erythromycin A.

Further preferred compounds of the invention include:

- 30 (11S,21S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(4-(pyridin-3-yl)-imidazol-1-yl)-ethylamino)-methylene]-erythromycin A;  
 (11S,21S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(quinolin-4-yl)-ethylamino)-methylene]-erythromycin A;  
 (11S,21S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(4-  
 35 (pyridin-3-yl)-imidazol-1-yl)-propylamino)-methylene]-erythromycin A;  
 (11S,21S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(quinoxalin-2-ylsulfanyl)-acetamido)-methylene]-erythromycin A;

- (11S, 21S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-4-oxo)-butyramido)-methylene]-erythromycin A;
- (11S,21S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(4-methoxy-3-nitro-phenyl)-4-oxo-butyramido)-methylene]-erythromycin A;
- 5 (11S,21S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(2-hydroxy-4,5-dimethoxy-phenyl)-4-oxo-butyramido)-methylene]-erythromycin A;
- (11S,21S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(4-oxo-4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl)-4-oxo-butyramido)-methylene]-erythromycin A;
- (11S,21S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(4-
- 10 quinolin-2-yl-1H-pyrazol-1-yl)propylamino)-methylene]-erythromycin A;
- (11S,21S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(3,4-dimethoxy-phenyl)-4-oxo-butyramido)-methylene]-erythromycin A;
- (11S, 21S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(4-hydroxy-3-methoxy-phenyl)-4-oxo-butyramido)-methylene]-erythromycin A;
- 15 (11S, 21S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(4-(thiophen-2-yl)-imidazol-1-yl)-propylamino)-methylene]-erythromycin A.

Compounds according to the invention also exhibit a broad spectrum of antibacterial activity against a wide range of clinical pathogenic microorganisms.

- 20 For example, using a standard microtiter broth serial dilution test, compounds of the invention have been found to exhibit useful levels of activity against a wide range of pathogenic microorganisms including *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Streptococcus pyogenes*, *Haemophilus influenzae*.
- Furthermore compounds of the invention are also active against intracellular pathogens such as *Chlamydia pneumonia*, *Chlamydia spp*, *Legionella pneumophila*, *Mycoplasma pneumonia*, species.
- 25

The compounds of the invention may therefore be used for treating a variety of diseases caused by pathogenic bacteria in human beings and animals.

- 30 Thus, according to another aspect of the present invention, we provide a compound of formula (I) or a physiologically acceptable salt thereof for use in the therapy in a human or animal subject.

- 35 According to a further aspect of the invention we provide the use of a compound of formula (I) or a physiologically acceptable salt thereof for the manufacture of a therapeutic agent for the treatment of systemic or topical bacterial infections in a human or animal body.

According to a yet further aspect of the invention we provide a method of treatment of the human or non-human animal body to combat bacterial infections which method comprises

administering to the body an effective amount of a compound of formula (I) or a physiologically acceptable salt thereof.

The term treatment is also meant to include prophylaxis.

5

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation.

10 The compounds of the invention may be formulated for administration in any convenient way for use in human or veterinary medicine and the invention therefore includes within its scope pharmaceutical compositions comprising a compound of the invention adapted for use in human or veterinary medicine. Such compositions may be presented for use in conventional manner with the aid of one or more suitable carriers or excipients. The compositions of the  
15 invention include those in a form especially formulated for parenteral, oral, buccal, rectal, topical, implant, ophthalmic, nasal or genito-urinary use.

The compounds according to the invention may be formulated for use in human or veterinary medicine by injection (e.g. by intravenous bolus injection or infusion or via intramuscular, subcutaneous or intrathecal routes) and may be presented in unit dose form, in ampoules, or  
20 other unit-dose containers, or in multi-dose containers, if necessary with an added preservative. The compositions for injection may be in the form of suspensions, solutions, or emulsions, in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, solubilising and/or dispersing agents. Alternatively the active  
25 ingredient may be in sterile powder form for reconstitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

The compounds of the invention may also be presented for human or veterinary use in a form suitable for oral or buccal administration, for example in the form of solutions, gels, syrups, mouth washes or suspensions, or a dry powder for constitution with water or other suitable  
30 vehicle before use, optionally with flavouring and colouring agents. Solid compositions such as tablets, capsules, lozenges, pastilles, pills, boluses, powder, pastes, granules, bullets or premix preparations may also be used. Solid and liquid compositions for oral use may be prepared according to methods well known in the art. Such compositions may also contain  
35 one or more pharmaceutically acceptable carriers and excipients which may be in solid or liquid form.

The compounds of the invention may also be administered orally in veterinary medicine in the form of a liquid drench such as a solution, suspension or dispersion of the active  
40 ingredient together with a pharmaceutically acceptable carrier or excipient.

The compounds of the invention may also, for example, be formulated as suppositories, e.g. containing conventional suppository bases for use in human or veterinary medicine or as pessaries e.g. containing conventional pessary bases.

5 The compounds according to the invention may be formulated for topical administration, for use in human and veterinary medicine, in the form of ointments, creams, gels, lotions, shampoos, powders, (including spray powders), pessaries, tampons, sprays, dips, aerosols, drops (e.g. eye ear or nose drops) or pour-ons.

10 Aerosol sprays are conveniently delivered from pressurised packs, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas.

For topical administration by inhalation the compounds according to the invention may be  
15 delivered for use in human or veterinary medicine via a nebuliser.

The pharmaceutical compositions for topical administration may also contain other active ingredients such as corticosteroids or antifungals as appropriate.

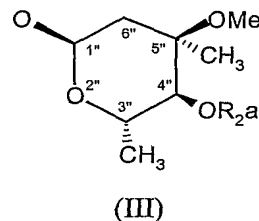
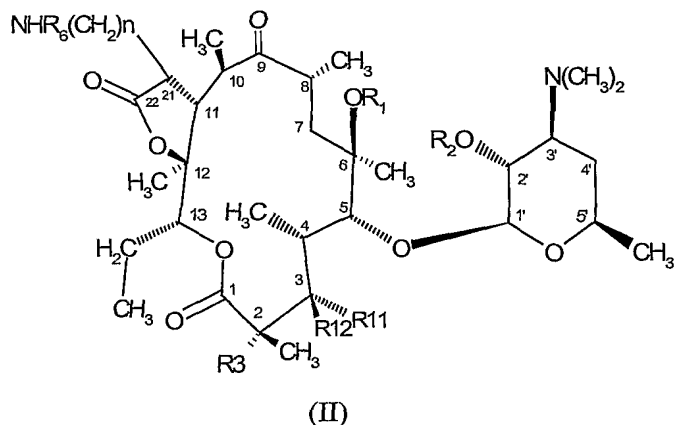
20 The compositions may contain from 0.01-99% of the active material. For topical administration, for example, the composition will generally contain from 0.01-10%, more preferably 0.01-1% of the active material.

For systemic administration the daily dose as employed for adult human treatment it will  
25 range from 2-100mg/kg body weight, preferably 5-60 mg/kg body weight, which may be administered in 1 to 4 daily doses, for example, depending on the route of administration and the condition of the patient. When the composition comprises dosage units, each unit will preferably contain 200 mg to 1 g of active ingredient.

The duration of treatment will be dictated by the rate of response rather than by arbitrary  
30 numbers of days.

Compounds of general formula (I) and salts thereof may be prepared by general method outlined hereinafter. In the following description, the groups R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub>, n, m, p, q, X, Y and A have the meaning defined for the compounds of formula (I)  
35 unless otherwise stated.

Compounds of formula (I), wherein A is -N(R<sub>6</sub>)C(O)- or a -N(R<sub>6</sub>)S(O<sub>2</sub>)-, may be prepared by reaction of compounds of formula (II)



- wherein  $R_{11}$  is a cladinose derivative of formula (III), in which  $R_{2a}$  is a hydroxy protecting group, or hydroxy,  $R_{12}$  is hydrogen or  $R_{12}$  together  $R_{11}$  is an oxygen atom, with a suitable activated derivative of the acid (IV),  $\text{HOC(O)XR}_4$  (IV) or with a suitable activated derivative of the sulfonic acid (V)  $\text{HOS(O)}_2\text{XR}_4$  (V) respectively and, if required, subjecting the resulting compound to one or more of the following operations a) hydrolysis of the cladinose derivative (III); b) conversion of the 3-hydroxy group into the 3-oxo; c) removal of the protecting group  $R_2$ .

Suitable activated derivatives of the carboxyl group or the sulphonic acid include the corresponding acyl halide, mixed anhydride or activated ester such as a thioester or a pentafluoroester.

- The reaction is preferably carried out in a suitable aprotic solvent such as halohydrocarbon (e.g. dichloromethane) or  $N,N$ -dimethylformamide optionally in the presence of a tertiary base such as pyridine, dimethylaminopyridine or triethylamine and at a temperature within the range of  $0^\circ$  to  $120^\circ\text{C}$ .
- Compounds of formula (I) wherein  $A$  is  $-\text{N(R}_6\text{)C(Y)N(R}_7\text{)}-$  and  $R_7$  is optionally substituted phenyl or  $\text{C}_{1-4}$  alkyl, may be prepared from compounds of formula (II), wherein  $R_{11}$  and  $R_{12}$  have the meaning defined above, by reaction with a compound of formula  $\text{R}_4\text{XNR}_7\text{C(Y)L}$  (VI), wherein  $L$  is a suitable leaving group as above defined and  $R_7$  is phenyl or  $\text{C}_{1-4}$  alkyl, if required, subjecting the resulting compound to one or more of the following operations a) hydrolysis of the cladinose derivative (III); b) conversion of the 3-hydroxy group into the 3-oxo and c) removal of the protecting group  $R_2$ .

- Compounds of formula (I) wherein  $A$  is  $-\text{N(R}_6\text{)C(Y)NH-}$  may be prepared from compounds of formula (II), wherein  $R_{11}$  and  $R_{12}$  have the meaning defined above by reaction with a compound of formula  $\text{R}_4\text{XN=C=Y}$  (VII), if required, subjecting the resulting compound to one or more of the following operations a) hydrolysis of the cladinose derivative (III); b) conversion of the 3-hydroxy group into the 3-oxo and c) removal of the protecting group  $R_2$ .

Compounds of formula (I) wherein A is  $-N(R_6)-$  may be prepared from compounds of formula (II), wherein  $R_{11}$  and  $R_{12}$  have the meaning defined above, by reaction with a compound of formula  $R_4XL$  (VIII), wherein L is a suitable leaving group.

If required, subjecting the resulting compound to one or more of the following operations a) hydrolysis of the cladinose derivative (III); b) conversion of the 3-hydroxy group into the 3-oxo and c) removal of the protecting group  $R_2$ .

Suitable leaving groups for this reaction include halogen (e.g. chlorine, bromine or iodine) or sulfonyl (e.g. tosyl or methansulfonyl).

- 10 Compounds of formula (I) wherein R is A is a  $N(R_6)C(O)O$  group, in which  $R_6$  is hydrogen, phenyl or  $C_{1-4}$  alkyl, may be prepared from compounds of formula (II), wherein  $R_{11}$  and  $R_{12}$  have the meaning defined above, by reaction with the appropriate haloformate compound of formula  $R_4XOC(O)L$  (IX) wherein L is a suitable leaving group such as halogen (e.g. chlorine or bromine) and, if required, subjecting the resulting compound to one or more of the following operations a) hydrolysis of the cladinose derivative (III); b) conversion of the 3-hydroxy group into the 3-oxo and c) removal of the protecting group  $R_2$ .

- 20 The reactions of compounds (II) with compounds (VI), (VII), (VIII) or (IX) are conveniently carried out in a solvent such as tetrahydrofuran, acetonitrile or halohydrocarbon (e.g. dichloromethane) optionally in the presence of a base such as triethylamine and at a temperature within the range  $0^\circ$  to  $80^\circ C$ .

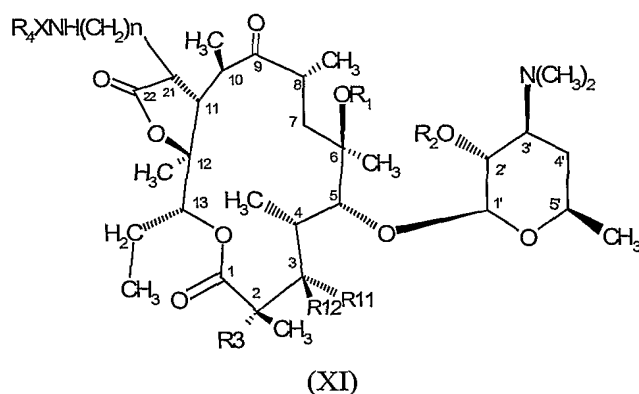
- 25 Compounds of formula (I) wherein A is a  $N=C(R_6)$  group, may be prepared from compounds of formula (II), wherein  $R_{11}$  is hydroxy,  $R_{12}$  is hydrogen or  $R_{11}$  together  $R_{12}$  is an oxygen atom, by reaction with a compound of formula  $R_4XCHO$  (X) and, if required, subjecting the resulting compound to one or more of the following operations a) conversion of the 3-hydroxy group into the 3-oxo and b) removal of the protecting group  $R_2$ .

- 30 The reaction is preferably carried out in a solvent such as a halohydrocarbon e.g. dichloromethane at a temperature within the range  $0^\circ$  to  $50^\circ C$ .

- 35 Compounds of formula (I), wherein A is  $N[C(O)R_6]$  may be prepared by treating a compound of formula (XI) in which  $R_{11}$  and  $R_{12}$  have the meaning as defined for compounds of formula (II), by acylation reaction with the activated carboxylic acid of formula (XIa)  $R_6COOH$  (XIa).



19

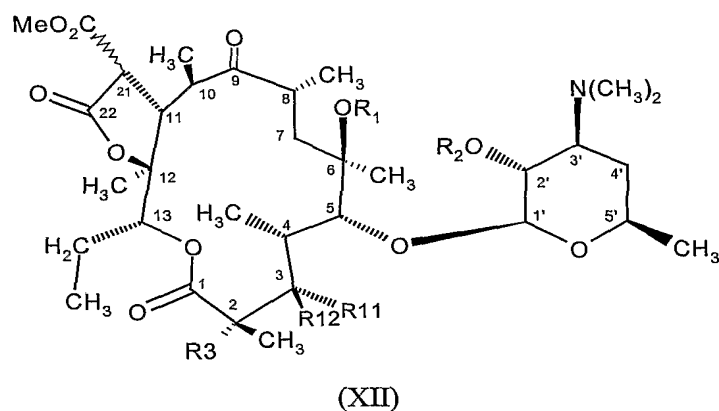


and, if required, subjecting the resulting compound to one or more of the following operations a) hydrolysis of the cladinoside derivative (III); b) conversion of the 3-hydroxy group into the 3-oxo and c) removal of the protecting group  $R_2$ .

The reaction is preferably carried out in the presence of a base such as a tertiary amine e.g. triethylamine or pyridine in a solvent such as a halohydrocarbon e.g. dichloromethane at a temperature within the range  $0^\circ$  to  $50^\circ\text{C}$ .

Suitable activated derivatives of the carboxyl group or the sulphonic acid include the corresponding acyl halide, mixed anhydride or activated ester such as a thioester or a pentafluoroester.

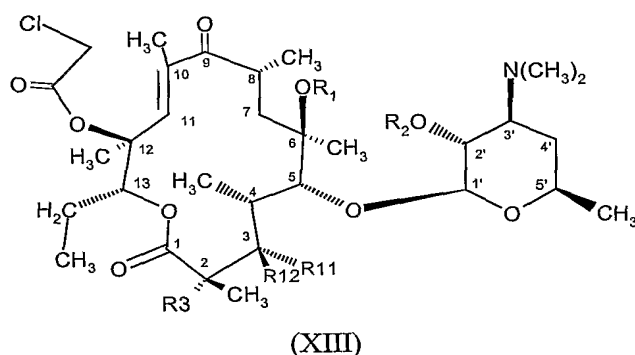
Compounds of formula (I) in which R is hydrogen may be prepared by decarboxylation of a compound of formula (XII), wherein  $R_{11}$  and  $R_{12}$  have the meaning as defined for compounds of formula (II), followed, if required, subjecting the resulting compound to one or more of the following operations a) hydrolysis of the cladinoside derivative (III); b) conversion of the 3-hydroxy group into the 3-oxo and c) removal of the protecting group  $R_2$ .



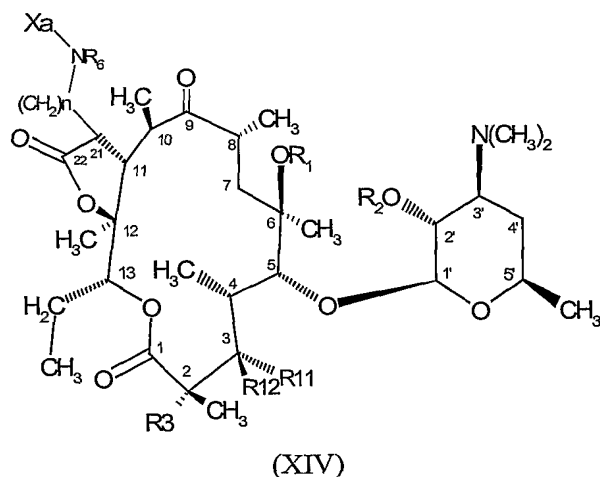
The decarboxylation may be carried out in the presence of a lithium salt such as lithium chloride, preferably in an organic solvent such as dimethylsulphoxide.

Compounds of formula (I), wherein R is cyano, may be prepared by cyclisation of chlorine derivatives (XIII) wherein R<sub>11</sub> and R<sub>12</sub> have the meaning as defined for compounds of formula (II),

5



- 10 with potassium cyanide and conveniently in the presence of a solvent such as a N-N dimethylformamide and, if required, subjecting the resulting compound to one or more of the following operations a) hydrolysis of the cladinoside derivative (III); b) conversion of the 3-hydroxy group into the 3-oxo and c) removal of the protecting group R<sub>2</sub>.
- 15 In a preferred embodiment of the invention, compounds of formula (I) in which A is -N(R<sub>6</sub>)- and X is C<sub>2-10</sub>alkylene interrupted by NR<sub>8</sub>-, -N(R<sub>8</sub>)C(Y)N(R<sub>9</sub>)-, -N(R<sub>8</sub>)C(O)- or -N(R<sub>8</sub>)C(O)C(O)-, may be prepared by reaction of a compound of formula (XIV),



20

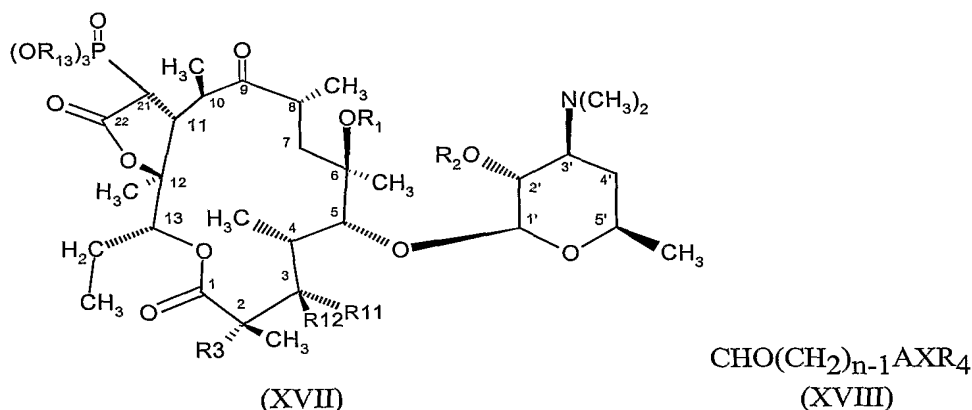
wherein Xa is C<sub>2-10</sub>alkyl-N(R<sub>8</sub>), R<sub>11</sub> and R<sub>12</sub> are defined as in formula (II), with compounds LXbR<sub>4</sub>(XV), in which L is a suitable leaving group, Xb is a group selected from C(Y)N(R<sub>9</sub>), C(Y)N(R<sub>9</sub>)C<sub>1-8</sub>alkylene, C(O), C(O)C<sub>1-8</sub>alkylene, C(O)C(O) or C(O)C<sub>1-8</sub>alkylene and, if required, subjecting the resulting compound to one or more of the following

25

operations a) hydrolysis of the cladinoside derivative (III); b) conversion of the 3-hydroxy group into the 3-oxo and c) removal of the protecting group R<sub>2</sub>.

Compounds of formula (XIV) may be prepared from compounds of formula (II) by reductive N-alkylation with a compound of formula HC(O)C<sub>2-9</sub>alkyl N(R<sub>6</sub>)(XVI). The reaction is conveniently carried in a protic solvent such as alcohol, i.e methanol, and in the presence of a suitable metal reducing agent such as sodium borohydride or sodium triacetoxyborohydride.

Compounds of formula (I) in which n is 2 or 3 and wherein X is optionally substituted and/or optionally substituted C<sub>1-10</sub> alkylene may be prepared from a phosphite of formula (XVII), wherein R<sub>11</sub> and R<sub>12</sub> have the meaning defined in formula (II) and R<sub>13</sub> is C<sub>1-4</sub> alkyl,



by Wittig-Horner reaction with an aldehyde of formula (XVIII), followed by reduction of the corresponding double bond using hydrogen and a metal catalyst (e.g. palladium) and, if required, subjecting the resulting compound to one or more of the following operations a) hydrolysis of the cladinoside derivative (III); b) conversion of the 3-hydroxy group into the 3-oxo and c) removal of the protecting group R<sub>2</sub>.

The Wittig-Horner reaction is carried out in the presence of a suitable organic or inorganic base such as 1,8-diazabicyclo[5.4.0]undec-7-ene or diisopropylethylamine in an aprotic solvent such as dichloromethane, preferably at a temperature ranging between -20° to +80°C.

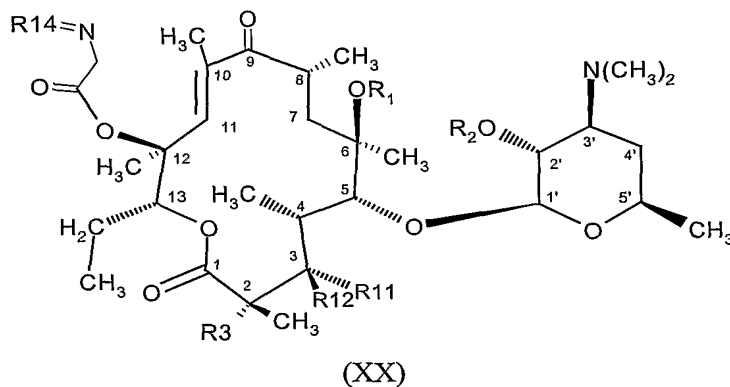
In the reactions described above cladinoside derivatives of formula (III) may be removed by treatment with an organic or inorganic acid. Example of a suitable inorganic acid is hydrochloride. The reaction is carried out in the presence of water or an organic solvent such as tetrahydrofuran, dichloromethane or mixture thereof.

In the reactions described above the conversion of the 3-hydroxy group into the 3-oxo may be performed by oxidation reaction using a modified Moffatt-Pfitzner procedure. Suitable oxidizing agent include N,N-Dimethylaminopropyl-3-ethyl carbodiimide - dimethylsulfoxide. The reaction is suitably carried out in the presence of pyridiniumtrifluoroacetate in a chlorinated solvent such as methylene chloride at -10°C to 25°C.

In a further embodiment, the oxidation may be carried out using Dess Martin periodinane reagent.

Compounds of formula (I), wherein A is  $\text{NR}_6$  and in which  $\text{R}_6$  is optionally substituted  $\text{C}_{1-4}$ alkyl, may be prepared by treating amino compounds of formula (II), wherein  $\text{R}_6$  is hydrogen, with an alkylating agent L- $\text{R}_6$  (XIX) wherein L is a suitable leaving group in the presence of a base.

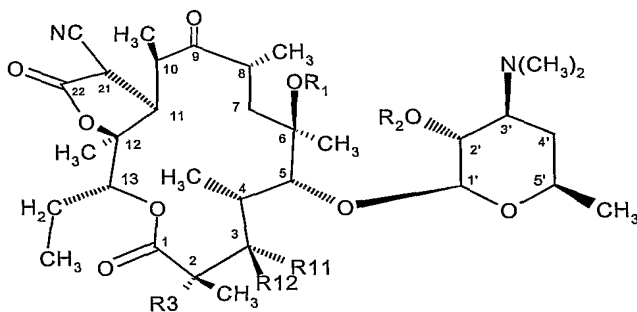
Compounds of formula (II) wherein n is 0 may be prepared by intramolecular Michael reaction of compounds of formula (XX) wherein  $\text{R}_{14}$  is a suitable nitrogen protecting group,  $\text{R}_{11}$  and  $\text{R}_{12}$  have the meaning defined in formula (II), in the presence of an organic base such as 1,8-diazabicyclo[5.4.0]undec-7-ene.



The reaction conveniently takes place in an aprotic polar solvent such as acetonitrile, dimethylformamide or an aqueous mixture thereof, followed by removal of the nitrogen protecting group  $\text{R}_{14}$ .

Suitable nitrogen protecting group  $\text{R}_{14}$  for use in this reaction includes diarylmethylidene such as diphenylmethylidene.

Compounds of formula (II) wherein n is 1 may be prepared by reduction of a compound of formula (XXI), wherein  $\text{R}_{11}$  and  $\text{R}_{12}$  have the meaning defined in formula (II).



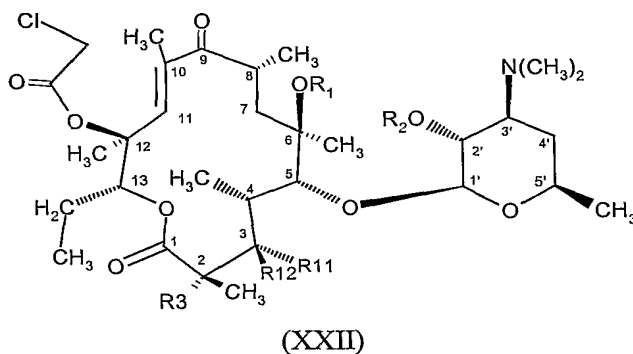
23

(XXI)

The reduction may be carried out using conventional reducing agents known in the art for converting a nitrile group into an amino group. Thus for example the reaction may be carried out using hydrogen in the presence of Raney-Nickel as catalyst.

The reaction is preferably carried out in an alcoholic solvent such as methyl, ethyl or isopropyl alcohol.

Compounds of formula (XXI) may be prepared by cyclisation of chlorine derivatives (XXII) wherein  $R_{11}$  and  $R_{12}$  have the meaning as defined for compounds of formula (II),

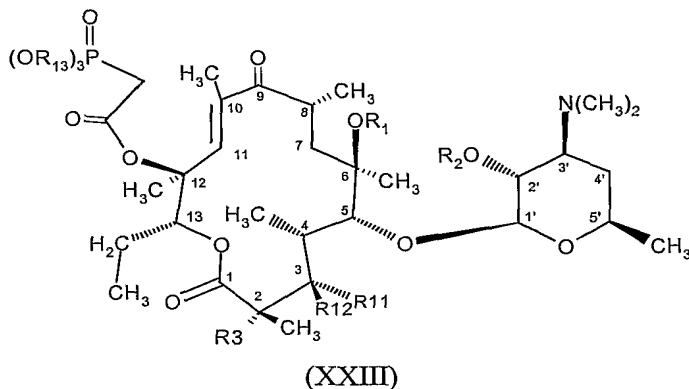


15

with potassium cyanide and conveniently in the presence of a solvent such as a N-N dimethylformamide, followed if required, subjecting the resulting compound to one or more of the following operations a) hydrolysis of the cladinoside derivative (III); b) conversion of the 3-hydroxy group into the 3-oxo and c) removal of the protecting group  $R_2$ .

20

Compounds of formula (XVII) may be prepared by heating a compound of formula (XXIII)



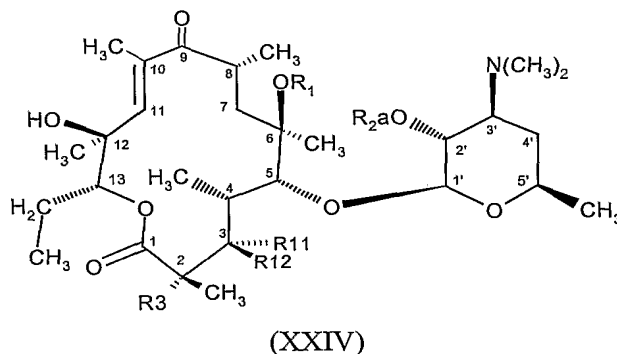
25

in an aprotic solvent such as N,N dimethylformamide at a temperature ranging from 60° to 120°C in the presence of a base such as 1,8-diazabicyclo[5.4.0]undec-7-ene.

Compounds of formula (XXIII) may be prepared by reaction of chlorine derivatives of formula (XXII) with  $(R_{13}O)_3$ phosphite. The reaction is carried out in a suitable aprotic solvent such as a hydrocarbon (i.e. toluene or xylene), N,N-dimethylformamide or by neat at a temperature within the range of 80° to 160°C.

5

Compounds of formula (XXII) may be prepared by reacting the corresponding hydroxy derivatives (XXIV),



10

wherein  $R_{11}$  and  $R_{12}$  have the meaning defined in formula (II), with a suitable activated derivative of the acid  $HOCOCH_2Cl$  (XXV).

Thus for example the esterification may be carried out by reaction with anhydride  $(ClCH_2CO)_2O$  (XXVI) in a suitable aprotic solvent such as a halohydrocarbon (e.g. dichloromethane) or N,N-dimethylformamide and in the presence of a tertiary base such as pyridine, dimethylaminopyridine or triethylamine and at a temperature within the range of 0°C to 120°C.

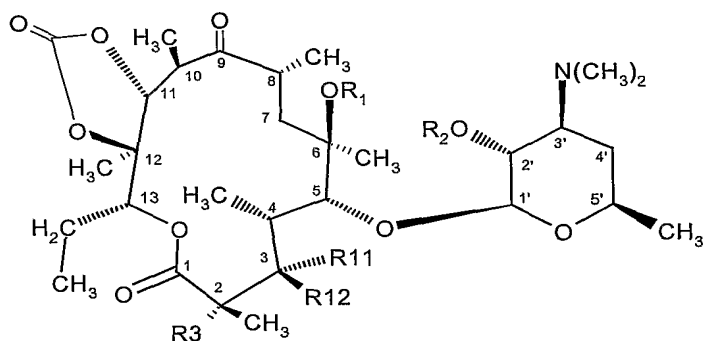
Compounds of formula (XX) may be prepared by treating a compound of formula (XXII) with sodium azide, subjecting the resulting azido compound to the following operations: a) reduction by conventional means for reducing azido group to amino group and b) conversion of the group  $NH_2$  into the nitrogen protecting group  $N=R_{14}$  wherein  $R_{14}$  has the meaning defined above and, if required, by removal of the hydroxy protecting group  $R_2$ .

The reduction to amino group may be carried out, for example, in the presence of triphenylphosphine and water.

In a further embodiment of the invention compounds of formula (XX) may be prepared by treating a compound of formula (XXII) with  $NH_4OH$  in the presence of solvent a suitable solvent for this reaction is dimethylsulphoxide and water.

Compounds of formula (XXIV), may be prepared by reacting 11,12-carbonate erythromycin A derivatives (XXVII),  $R_{11}$  and  $R_{12}$  have the meaning defined in formula (II), with a strong base such as 1,8 diazabicyclo [5.4.0]undec-7-ene.

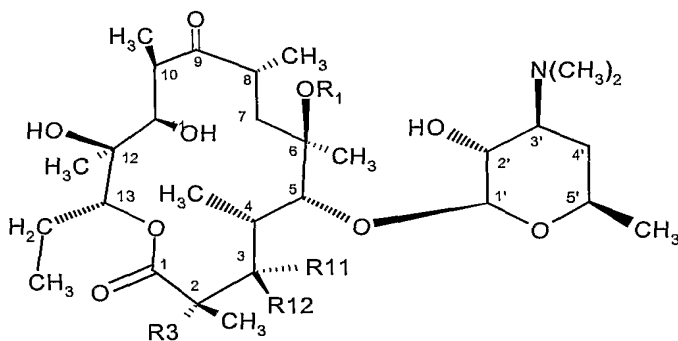
25



(XXVII)

The elimination reaction may be carried out in an organic solvent such toluene, ethyl acetate, N,N dimethylformamide or a mixture thereof, conveniently with heating.

- 5 Compounds of formula (XXVII), may be prepared from erythromycin A derivatives of formula (XXVIII),



(XXVIII)

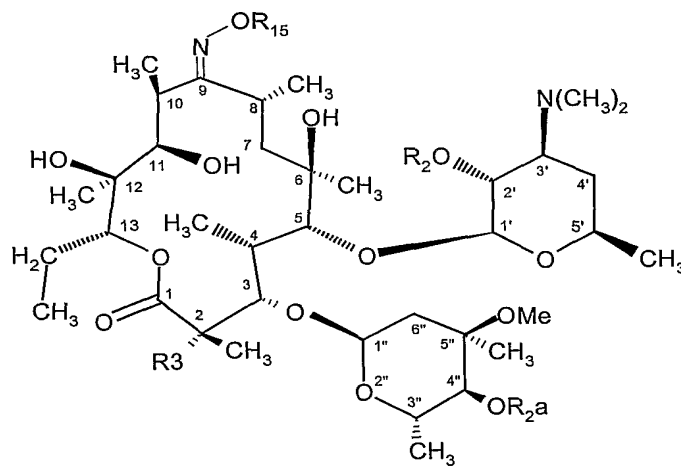
10

by conversion of the 2'- hydroxy group into the corresponding hydroxy protected group and by conversion of the 11, 12 hydroxy into a carbonate group using triphosgene in a suitable solvent such as dichloromethane, in the presence of pyridine.

15

- Compounds of formula (XXVIII), may be prepared by alkylation of an oxime of formula (XXIX)

26



(XXIX)

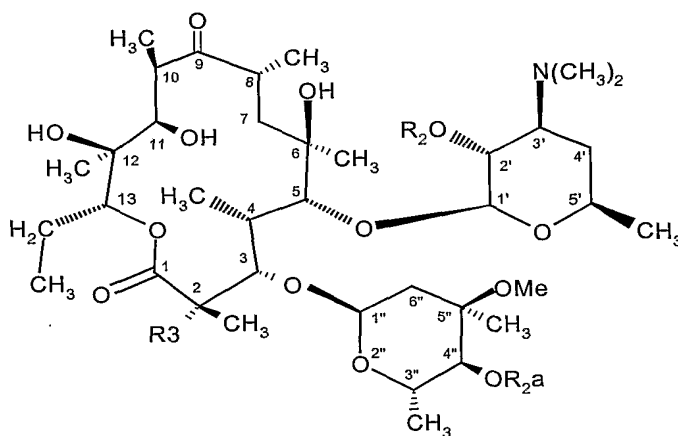
wherein R<sub>15</sub> is oxime protecting group and R<sub>2</sub> and R<sub>2a</sub> are a hydroxyl protecting group, with  
 5 a compound of formula L-R<sub>1</sub> (XXX) in which L is a suitable leaving group such as a halogen (e.g. chlorine, bromine or iodine) or a sulfonyl (e.g. tosyl, methanesulfonyl), in the presence of a base, followed by hydrolysis of cladinose derivative and conversion of the 3-hydroxy group into the 3-oxo.

The reaction with compound (XXX) is preferably carried out in a solvent such as a  
 10 halohydrocarbon (e.g. dichloromethane), an ether (e.g. tetrahydrofuran, dimethoxyethane), acetonitrile and the like.

Examples of the bases which may be used include potassium hydroxide, cesium hydroxide, tetraalkylammonium hydroxide, sodium hydride, potassium hydride and the like, followed by subsequent removal of oxime protecting group.

15 A suitable oxime protecting group is R<sub>15</sub>, for example, 1-isopropoxycyclohex-1-yl.

Oxime compounds (XXIX) may be prepared by reaction of a compound of formula (XXXI) wherein R<sub>2</sub> and R<sub>2a</sub> are hydrogen, using analogous methods to those described in USP 6110965.



(XXXI)

20



Compounds of formula (I) wherein  $R_3$  is halogen may be prepared from compounds of formula (I) in which  $R_3$  is hydrogen and  $R_2$  is hydroxy protecting group by reaction with a halogenating agent in the presence of an organic or inorganic base.

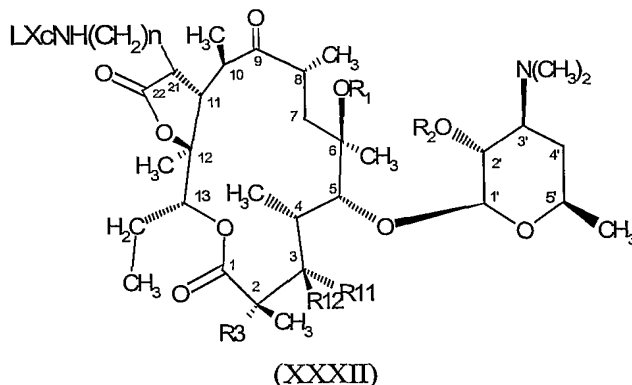
Suitable halogenating agents include N-fluoro benzensulfonimide, SELECTFLUOR™ for fluorination, pyridinium tribromide or cyanogen bromide for bromination or hexachloroethane for chlorination.

A convenient base for the reaction is selected from sodium hydride, potassium hydride, sodium carbonate, potassium hexamethyldisilazide, lithium diisopropylamide or pyridine.

The reaction is carried out in a solvent such as N,N dimethylformamide, tetrahydrofuran or N-methylpyrrolidone or a mixture thereof, conveniently at a temperature within the range -78° to 60°C.

Alternatively the halo group in position 2 of the macrolide ring may be introduced in an earlier step of the synthesis of compounds of formula (I). Thus, for example, it may be introduced by treating a compound of formulas (II), (IX), (XII), (XV), (XVI), (XVII), (XVIII), (XIX), (XXII) or (XXIII) provided that  $R_{11}$  together with  $R_{12}$  is an oxygen atom, using the method above described for obtaining compound (I) wherein  $R_3$  is a halo group.

Compounds of formula(I) wherein R is  $(CH_2)_nR_5$  may be prepared by intramolecular cyclisation of a compound of formula (XXXII),

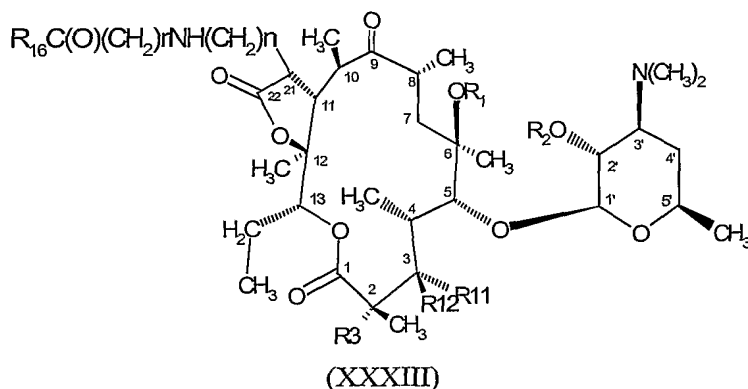


wherein L is suitable leaving group such halogen (i.e chlorine or bromine), X is C<sub>4-5</sub> alkylene chain optionally substituted by one or two groups selected from oxo 9 or 10 membered fused bicyclic heterocyclic having at least one heteroatom selected from oxygen, sulphur or nitrogen.

The reaction is suitable carried out in the presence of an inorganic base or an organic base.

Alternatively compounds of formula (I) wherein R is  $(CH_2)_nR_5$  may be prepared by intramolecular reductive N-alkylation of a compound of formula (XXXIII)

28



wherein  $R_{16}$  is 9 to 10 membered fused heterocyclic groups,  $r$  is 3 or 4. This reaction was carried out conveniently in an aprotic solvent such as dichloroethane and in the presence of a suitable metal reducing agent such as sodium borohydride or sodium triacetoxyborohydride.

Compounds of formulas (IV), (V), (VI), (VII), (VIII), (IX), (X), (XIa), (XIII), (XVI), (XVIII), (XIX), (XXI) or (XXV) are known or commercially available compounds or they may be prepared using methods known in the art.

The nitrogen protection reaction may be carried out with an appropriate imine such as benzophenone imine in an aprotic solvent e.g. dichloromethane preferably at room temperature.

Where it is desired to isolate a compound formula (I) as a salt thereof, for example a pharmaceutically acceptable salt, this may be achieved by reacting the compound of formula (I) in the form of the free base with an appropriate amount of suitable acid and in a suitable solvent such as an alcohol (e.g. ethanol or methanol), an ester (e.g. ethyl acetate) or an ether (e.g. diethyl ether or tetrahydrofuran).

Pharmaceutically acceptable salts may also be prepared from other salts, including other pharmaceutically acceptable salts, of the compound of formula (I) using conventional methods.

Suitable hydroxy protecting reagent are those described by T.W. Greene and P.G.M Wuts in Protective Groups in Organic Synthesis 2<sup>nd</sup> ed., John Wiley & Son, Inc 1991, which is incorporated by reference. Examples of suitable hydroxy protecting reagents include acetic anhydride, benzoic anhydride or a trialkylsilyl chloride in a protic solvent. Examples of aprotic solvent are dichloromethane, NN-dimethylformamide, dimethylsulfoxide, tetrahydrofuran and the like.

The hydroxyl protecting groups may be removed by well known standard procedures. For example when R<sub>2a</sub> is a trialkylsilyl group, this may be removed by treatment with tetrabutylammonium fluoride and acetic acid or by reaction with fluoride ions source such as triethyl amine tris (hydrogen fluoride) or this process is conveniently carried out in a solvent such as tetrahydrofuran or acetonitrile. When R<sub>2</sub> or R<sub>2a</sub> is alkanoyl (i.e acetyl or benzoyl) these may be removed by treatment with an alcohol (e.g. methanol or ethanol).

In any of the formulae (I), (II), (XI), (XIV), (XVII), (XXI), (XXXII) or (XXXIII) shown above when there is a an asymmetric carbon atom and no specific configuration is shown then the formula includes all possible configurations.

Specific stereoisomers of the compounds of formula (I) as defined in formula 1a and 1b essentially free of the other stereoisomers may be prepared using general processes described above starting with the appropriate stereoisomer of formula (II).

The process described above for preparing the compounds of formula (II) will in general give a mixture of diastereoisomers.

The individual stereoisomers of the compounds of formula (II) may be separated each other by conventional techniques such as fractional crystallisation or more particularly by column chromatography, using for example a silica column.

In a preferred embodiment of the invention the individual stereoisomer of formula (1a) wherein R is NH<sub>2</sub> may be prepared by epimerisation reaction of a compound of formula (1b) or mixture of (1a) and (1b) wherein R is NH<sub>2</sub>. The reaction is carried out in the presence of benzaldehyde and DBU, followed by hydrolysis of the imine derivative with inorganic acid such as hydrochloride. The reaction is suitable carried out in aprotic solvent such as for example toluene, N-N dimethylformamide.

The assignment of the R or S configuration at the 21-position have been made according to the rules of Cahn, Ingold and Prelog, *Experientia* 1956, 12, 81.

When examples are obtained as a diastereoisomeric mixture of 21R and 21S, unless otherwise stated, the <sup>1</sup>H-NMR spectra refers to the <sup>1</sup>H-NMR spectra of the predominant diastereoisomer (i.e. 21 S).

In the Intermediates and Examples unless otherwise stated:

Proton Magnetic Resonance (<sup>1</sup>H-NMR) spectra were recorded at 500 MHz, chemical shifts are reported in ppm downfield (δ) from Me<sub>4</sub>Si, used as internal standard, and are assigned as singlets (s), doublets (d), doublets of doublets (dd), triplets (t), quartets (q) or multiplets (m). Mass spectra were acquired with a Hewlett Packard 1100 MSD system equipped with a binary pump (Agilent Technologies), operating in positive electrospray ionisation mode.

LC/MS (Liquid Chromatography/Mass Spectroscopy) data were obtained by using a HP 1100 LC system (Agilent Technologies) equipped with a Sedex Evaporative Light Scattering Detector model 75 (Sedere) coupled with a Platform LCZ Mass Spectrometer (Micromass) operating in positive electrospray ionisation mode. The chromatographic analysis conditions

were: column Waters XTerra MS C18 (4.6 x 30mm, 2.5µm); flow rate 0.8ml/min; mobile phase: aqueous solution of NH<sub>4</sub>OAc (10mM, pH 6.8) (A) and acetonitrile (B).

LC (Liquid Chromatography) purifications were performed with a Waters 600 semi-preparative system equipped with a binary pumping system and a Jasco-UV detector. The chromatographic analysis conditions were: column Supelcosil ABZ+Plus (10cm x 21.2mm, 5µm); flow rate 8ml/min; mobile phase: aqueous solution of NH<sub>4</sub>OAc (10mM, pH 6.8) (A) and acetonitrile (B).

Column chromatography was carried out over silica gel 60 (230-400 mesh ASTM - Merck AG Darmstadt, Germany). The TLC (Thin Layer Chromatography) monitoring was performed using Merck 60 F<sub>254</sub> as TLC plate.

Phase separations were done by using Microfiltration Device - Filter Tube with polypropylene support (Whatman).

Resin washings were carried out on Extract-clean Tube (Alltech).

Purifications of crude products were performed by SCX-cartridges (Varian).

PS-Trisamina resin (polystyrene based) (Argonaut Technologies Inc.) was used to remove the excess of reagents.

Abbreviations which have been used in the description of the synthetic methods that follow are: Brine for aqueous saturated solution of sodium chloride, DBU 1,8-diazabicyclo[5.4.0]undec-7-ene, DCE for 1,2-dichloroethane, DCM for dichloromethane, DIPEA for N,N-diisopropylethylamine, DMAP for 4-dimethylaminopyridine, DMF for N,N-dimethylformamide, DMSO for methyl sulfoxide, EDC for 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, Et<sub>2</sub>O for diethyl ether, EtOAc for ethyl acetate, HATU for O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, HOBT for 1-hydroxybenzotriazole hydrate, iPrOH for 2-propanol, MeOH for methanol, MTBE for *tert*-butyl methyl ether, TEA for triethylamine and THF for tetrahydrofuran, wt for weight.

### **Intermediate 1**

#### **2'-O-Acetyl-11,12-carbonate-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-erythromycin A**

To a solution of 2'-O-acetyl-3-decladinosyl-6-O-methyl-3-oxo-erythromycin A (0.500g) in anhydrous DCM (20mL) under nitrogen atmosphere, pyridine (1.5mL) and phosgene (20% sol. in toluene, 1mL) were sequentially added. The reaction mixture was stirred overnight at room temperature then quenched with a saturated NaHCO<sub>3</sub> aqueous solution (50mL). The organic phase was washed with water (50mL), dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure and the crude product purified by flash chromatography (eluting with: DCM/MeOH 90/10) to give the title compound (0.360g).  
TLC: DCM/MeOH 90/10 (R<sub>f</sub>=0.6).

**Intermediate 2****2'-O-Acetyl-3-decladinosyl-11-deoxy-10,11-didehydro-6-O-methyl-3-oxo-erythromycin****A**

To a solution of intermediate 1 (0.210g) in 2\1 mixture of EtOAc\toluene (6mL), DBU (0.05mL) was added and the mixture was heated to 85°C for 6h. The reaction mixture was allowed to reach room temperature, the solvent evaporated and the crude product purified by flash chromatography (eluting with: DCM\MeOH 90\10) to give the title compound (0.150g). TLC: DCM\MeOH 90\10 (Rf=0.7).

**Intermediate 3****2'-O-Acetyl-12-chloroethanoyl-3-decladinosyl-11-deoxy-10,11-didehydro-6-O-methyl-3-oxo-erythromycin A**

To a solution of intermediate 2 (0.150g) in anhydrous DCM (3mL) cooled to 0°C, pyridine (0.05mL), chloroacetic anhydride (0.065g) and DMAP (5mg) were sequentially added under nitrogen atmosphere. The reaction mixture was stirred for 4h then quenched with water (10mL) and extracted with DCM (2x10mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure and the crude material purified by flash chromatography (eluting with: DCM\MeOH 80\20) to give the title compound (0.060g). TLC: DCM\MeOH 90\10 (Rf=0.8).

**Intermediate 4****(11S,21R)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(iminomethyl)-methylenel]-erythromycin A**

To a solution of example 1 (0.137g) in iPrOH (20mL) Raney-Nickel (0.100g) was added. The reaction mixture was saturated with hydrogen (5atm) and stirred at room temperature for 24h. After removing the catalyst by filtration and evaporating the solvent under reduced pressure, the crude material was purified by flash chromatography (eluting with: DCM\MeOH 95\5) to give the title compound (0.012g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.61, 7.07 (t+t, 1H), 4.94, 4.82 (dd+dd, 1H), 4.76 (m, 1H), 4.39, 4.38 (d+d, 1H), 4.24, 4.22 (d+d, 1H), 3.83 (q, 1H), 3.55 (m, 1H), 3.26 (m, 1H), 3.13 (m, 1H), 3.02, 2.90 (d+d, 1H), 2.96 (m, 1H), 2.70 (m, 1H), 2.65, 2.64 (s+s, 3H), 2.60, 2.50 (m+m, 1H), 2.26 (s, 6H), 2.07, 2.06 (s+s, 3H), 1.94 (m, 1H), 1.77-1.64 (m, 2H), 1.55 (m, 1H), 1.50, 1.46 (s+s, 3H), 1.33 (d+d, 6H), 1.32 (s, 3H), 1.21 (d, 3H), 1.17 (m, 1H), 1.14 (s, 3H), 0.97, 0.96 (d+d, 6H), 0.83, 0.80 (t+t, 3H).

TLC: DCM\MeOH 95\5 (Rf= 0.65).

**Intermediate 5****(11S,21R)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(iminomethyl)-methylenel]-erythromycin A**

A solution of intermediate 4 (0.010g) in MeOH (1mL) was stirred for 48h, then concentrated under reduced pressure to give the title compound (0.009g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.61, 7.09 (t+t, 1H), 4.94, 4.83 (dd +dd, 1H), 4.86 (bm, 1H), 4.32, 4.30 (d+d, 1H), 4.26, 4.24 (d+d, 1H), 3.86 (m, 1H), 3.56 (m, 1H), 3.13-3.10, 2.96 (m, 3H) 3.02 (m, 1H), 2.88 (bs, 1H), 2.66 (s, 3H), 2.50 (m, 1H), 2.30 (s, 6H), 1.95 (m, 1H), 1.85, 1.76 (m, 1H), 1.70-1.60 (m, 2H), 1.55 (m, 1H), 1.49, 1.46 (s+s, 3H), 1.4-1.3 (m, 6H), 1.30-1.14 (m, 2H), 1.0-0.9 (d, 3H), 0.84, 0.81 (t+t, 3H).  
TLC: DCM/MeOH 95/5 (R<sub>f</sub> = 0.45).

#### **Intermediate 6**

##### **2',4''-O-Diacetyl-6-O-methyl-erythromycin A**

- 10 To a solution of 6-O-methyl-erythromycin A (50g) in anhydrous DCM (240mL), TEA (26.1mL), DMAP (0.392g) and acetic anhydride (15.2mL) were added at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 0°C for 45min and overnight at room temperature. The mixture was then diluted with a saturated NH<sub>4</sub>Cl aqueous solution (240mL) and extracted with DCM (2x200mL). The aqueous phase was neutralised with a saturated  
15 NaHCO<sub>3</sub> aqueous solution and extracted again with DCM (2x200mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give the title compound (50.7g).  
m/z ([MH]<sup>+</sup>) = 832.

#### **Intermediate 7**

##### **11,12-Carbonate-2',4''-O-diacetyl-11,12-dideoxy-6-O-methyl-erythromycin A**

- To a solution of intermediate 6 (200g) in anhydrous DCM (1600mL) cooled to 0°C, pyridine (117mL) and a solution of triphosgene (71.2g) in anhydrous DCM (400mL) were added under nitrogen atmosphere. The resulting mixture was stirred at 0°C for 30min and then at room  
25 temperature for 15h. The mixture was then diluted with water (750mL) and extracted with DCM (2x500mL). The organic layer was washed with water (3x300mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give the title compound (200g).  
m/z ([MH]<sup>+</sup>) = 858.

#### **Intermediate 8**

##### **11-Deoxy-2',4''-O-diacetyl-10,11-didehydro-6-O-methyl-erythromycin A**

- To a solution of intermediate 7 (50.5g) in a 2/1 mixture of toluene/EtOAc (675mL), DBU (12mL) was added at room temperature. The resulting mixture was stirred at 85°C for 8h and at room temperature for 5h. The reaction mixture was then diluted with brine (250mL),  
35 extracted with EtOAc (2x350mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated under reduced pressure and the crude material purified by crystallisation (from acetone/water) to give the title compound (46g).  
m/z ([MH]<sup>+</sup>) = 814.

#### **Intermediate 9**

##### **12-Chloroethanoyl-11-deoxy-2',4''-O-diacetyl-10,11-didehydro-6-O-methyl-erythromycin A**

To a solution of intermediate **8** (20g) in anhydrous DCM (340mL) cooled to 0°C pyridine (6mL) and chloroacetic anhydride (8.4g) were added under nitrogen atmosphere and the reaction was allowed to reach room temperature. After 16h the reaction mixture was washed with water (300mL), a saturated NH<sub>4</sub>Cl aqueous solution (150mL) and brine (150mL) then extracted with DCM (2x300mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was dissolved in acetone (50mL) and water (100mL) was added under vigorous stirring. The precipitate was filtered and dried *in vacuo* to give the title compound (20.4g).

m/z ([MH]<sup>+</sup>) = 890.

#### Intermediate 10

##### 2'-O-Acetyl-12-chloroethanoyl-3-decladinosyl-11-deoxy-10,11-didehydro-6-O-methyl-erythromycin A

To a solution of intermediate **9** (20.2g) in THF (200mL) cooled to 0°C a 3N HCl aqueous solution (400mL) was added dropwise. The reaction mixture was allowed to reach room temperature and stirred overnight. The solution was neutralised with a saturated NaHCO<sub>3</sub> aqueous solution and extracted with DCM (2x200mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure and the crude material purified by quick filtration on silica gel (eluting with: DCM/MeOH 95\5) to give the title compound (15.4g).

m/z ([MH]<sup>+</sup>) = 690.

#### Intermediate 11

##### (11S,21R)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-6-O-methyl-12,11-[oxycarbonyl-(cyano)-methylene]-erythromycin A

To a solution of intermediate **10** (0.400g) in anhydrous DMF (30mL) potassium cyanide (0.380g) was added under nitrogen atmosphere. The mixture was stirred at room temperature for 2h, quenched with a saturated NaHCO<sub>3</sub> aqueous solution (50mL) and extracted with DCM (70mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure and the crude material purified by flash chromatography (eluting with: DCM/MeOH 90\10) to give the title compound (0.430g).

TLC: DCM/MeOH 90\10 (R<sub>f</sub>=0.50).

#### Intermediate 12

##### (11S,21R)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-6-O-methyl-12,11-[oxycarbonyl-(iminomethyl)-methylene]-erythromycin A

and

#### Intermediate 13

##### (11S,21R)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-6-O-methyl-12,11-[oxycarbonyl-(aminomethyl)-methylene]-erythromycin A

To a solution of intermediate **11** (0.100g) in iPrOH (10mL) Raney-Nickel (0.100g) was added. The mixture was saturated with hydrogen (5atm) and stirred at room temperature for 24h. After removing the catalyst by filtration and evaporating the solvent, the crude product

was purified by flash chromatography (eluting with: DCM/MeOH 90/10) to give the title compound 12 (0.038g) and the title compound 13 (0.027g).

TLC: DCM/MeOH 90/10, Rf (intermediate 12) = 0.43

TLC: DCM/MeOH 90/10, Rf (intermediate 13) = 0.2

5

#### **Intermediate 14**

#### **(11S,21R)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-6-O-methyl-12,11-[oxycarbonyl-(chloroacetamidomethyl)-methylene]-erythromycin A**

To a solution of intermediate 13 (0.054g) in anhydrous DCM (2mL) pyridine (0.010mL), chloroacetic anhydride (0.016g) and DMAP (catalytic amount) were sequentially added under nitrogen atmosphere. The mixture was stirred at 0°C for 1h. The reaction was quenched with a saturated NaHCO<sub>3</sub> aqueous solution (5mL) and extracted with DCM (10mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH 98/2) to give the title compound (0.036g).

15

TLC: DCM/MeOH 90/10 (Rf=0.43).

#### **Intermediate 15**

#### **(11S,21R)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-6-O-methyl-12,11-[oxycarbonyl-(chlorobutyramidomethyl)-methylene]-erythromycin A**

20

To a solution of intermediate 13 (0.100g) in anhydrous DCM (4mL) pyridine (0.024mL), 4-chlorobutyryl chloride (0.016mL) and DMAP (catalytic amount) were sequentially added under nitrogen atmosphere. The mixture was stirred at 0°C for 2h. The reaction was quenched with a saturated NaHCO<sub>3</sub> aqueous solution (10mL) and extracted with DCM (20mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure and the crude material purified by flash chromatography (eluting with: DCM/MeOH 95/5) to give the title compound (0.100g).

25

TLC: DCM/MeOH 90/10 (Rf=0.40).

m/z ([MH]<sup>+</sup>) = 789.

30

#### **Intermediate 16**

#### **2'-O-Acetyl-12-aminoethanoyl-3-decladinosyl-11-deoxy-10,11-didehydro-6-O-methyl-erythromycin A**

To a solution of intermediate 10 (3g) in DMSO (40mL) a 32% aqueous ammonia solution (8mL) was added dropwise over 10min at room temperature. The reaction mixture was stirred for 2h at 50°C. After cooling to 0°C, water (40mL) was added and the mixture was extracted with MTBE (2x45mL). The collected organic layers were washed with brine (40mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give the title compound (2.5g).

35

TLC: DCM/MeOH 10/1 (Rf=0.28).

40



**Intermediate 17****2'-O-Acetyl-12-(benzhydrylidene)-aminoethanoyl-3-decladinosyl-11-deoxy-10,11-didehydro-6-O-methyl-erythromycin A**

A solution of intermediate 16 (4.0g) and benzophenone imine (2.6mL) in anhydrous DCM (40mL) was stirred at room temperature under nitrogen atmosphere. After 36h the reaction was quenched with water (100mL) and extracted with DCM (3x300mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure and the crude material purified by flash chromatography (eluting with: DCM/MeOH 95/5) to give the title compound (3.5g). TLC: DCM/MeOH 10/1 (R<sub>f</sub>=0.38).

**Intermediate 18****(11S,21R,S)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-6-O-methyl-12,11-oxycarbonyl-(benzhydrylideneamino)-methylenel-erythromycin A**

A solution of intermediate 17 (3.0g) and DBU (0.540mL) in acetonitrile (135mL) and water (15mL) was stirred at room temperature for 3h. After evaporating the solvent, the crude material was dissolved in DCM (300mL) and washed with water (100mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give the title compound (3.0g).

TLC: DCM/MeOH 10/1 (R<sub>f</sub>=0.38).

**Intermediate 19****11-Deoxy-2',4''-O-diacetyl-10,11-didehydro-12-methoxycarbonylethanoyl-6-O-methyl-erythromycin A**

To a solution of intermediate 8 (0.500g) in anhydrous toluene (100mL) under nitrogen atmosphere, pyridine (0.250mL) and methylmalonyl chloride (0.158mL) were added at 0°C. The temperature was allowed to reach room temperature. After stirring for 1h, water (50mL) was added, the organic layer was washed with brine (50mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated under reduced pressure and the crude material purified by quick filtration on silica gel to give the title compound (0.560g).

m/z ([MH]<sup>+</sup>) = 914.

**Intermediate 20****2'-O-Acetyl-3-decladinosyl-11-deoxy-10,11-didehydro-12-methoxycarbonylethanoyl-6-O-methyl-erythromycin A**

and

**Intermediate 21****2'-O-Acetyl-3-decladinosyl-11-deoxy-10,11-didehydro-12-carboxyethanoyl-6-O-methyl-erythromycin A**

A solution of intermediate 19 (0.500g) in a 2N HCl aqueous solution (50mL) and THF (1mL) was stirred at room temperature for 6h. Then, the mixture was cooled to 0°C and a saturated potassium carbonate aqueous solution was added until pH= 9 was obtained. The mixture was

extracted with DCM (2x50mL), the organic phase washed with brine (25mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH = 95/5) to give the title compound 20 (0.180g), and the title compound 21 (0.180g).

- 5 m/z ([MH]<sup>+</sup>) (intermediate **20**) = 714.  
m/z ([MH]<sup>+</sup>) (intermediate **21**) = 700.

#### Intermediate 22

- 10 (10R,S,11S,21R,S)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-6-O-methyl-12,11-  
[oxycarbonyl-(methoxycarbonyl)-methylene]-erythromycin A

- A solution of intermediate **20** (0.150g) and DBU (0.050mL) in water (1.5mL) and acetonitrile (13.5mL) was stirred at 40°C for 6h. After evaporating the solvent under reduced pressure, the residue was dissolved in DCM (20mL), the organic phase washed with water (50mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduce pressure. The crude material was purified  
15 by flash chromatography (eluting with: DCM/MeOH 95/5) to give the title compound (0.070g).  
m/z ([MH]<sup>+</sup>) = 714.

#### Intermediate 23

- 20 (10R,S,11R)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-6-O-methyl-12,11-  
[oxycarbonylmethylene]-erythromycin A

- A mixture of intermediate **22** (0.050g) and lithium chloride (0.006g) in DMF (1mL) was heated to reflux for 4h. The mixture was allowed to reach room temperature and poured into a 3% NaHCO<sub>3</sub> aqueous solution at 0°C, then extracted with DCM (2x15mL). The organic phase  
25 was washed with water (2x10mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was vpurified by flash chromatography (DCM/MeOH: 95/5) to give the title compound (0.010g).  
m/z ([MH]<sup>+</sup>) = 656.

- 30 Intermediate 24

#### (11S,21S)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11- [oxycarbonyl-(2-(chloro)-ethylamino)-methylene]-erythromycin A

- To a solution of example **7** (0.335g) in anhydrous acetonitrile (3mL) chloroacetaldehyde (50 wt % solution in water, 0.127mL) was added under a nitrogen atmosphere and the resulting  
35 mixture was stirred for 20h at room temperature. Sodium cyanoborohydride (1M in THF, 0.500mL) and acetic acid (0.041mL) were added and the reaction mixture was stirred for 6h at room temperature. After evaporating the solvent the residue was dissolved in DCM (25mL) and washed with a 5% NaHCO<sub>3</sub> aqueous solution (10mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give the title compound (0.300g).  
40 m/z ([MH]<sup>+</sup>) = 731.

#### Intermediate 25

**(11S,21R)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-6-O-methyl-12,11-[oxycarbonyl-(3-quinolinyl-carbonylaminomethyl)-methylene]-erythromycin A**

To a solution of intermediate 13 (0.028g) in anhydrous DMF (2.5mL) 3-quinolinecarboxylic acid (0.008g), HATU (0.017g) and DIPEA (0.017mL) were sequentially added under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 4h and then the solvent evaporated under vacuum. The residue was dissolved in DCM (15mL) and washed with water (10mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude product was purified by flash chromatography to give the title compound (0.022g).  
TLC: DCM/MeOH 90/10 (Rf=0.37).

**Intermediate 26**

**(11S,21R)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-6-O-methyl-12,11-[oxycarbonyl-(4-(4-(pyridin-3-yl)-imidazol-1-yl)-butyramidomethyl)-methylene]-erythromycin A**

To a solution of intermediate 13 (0.050g) in anhydrous DMF (5mL) intermediate 49 (0.019g), HATU (0.030g) and DIPEA (0.031mL) were sequentially added under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 3h, and then the solvent was removed under vacuum. The residue was dissolved in DCM (20mL), the organic phase washed with water (15mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography to give the title compound (0.042g).  
TLC: DCM/MeOH 90/10 (Rf=0.37).

**Intermediate 27**

**(11S,21R)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-6-O-methyl-12,11-[oxycarbonyl-(3-(4-(pyridin-3-yl)-imidazol-1-yl)-propionamidomethyl)-methylene]-erythromycin A**

To a solution of intermediate 13 (0.050g) in anhydrous DMF (5mL) intermediate 48 (0.020g), HATU (0.030g) and DIPEA (0.031mL) were sequentially added under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 4h and then the solvent was removed under vacuum. The residue was dissolved in DCM (15mL), the organic phase washed with water (10mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude product was purified by flash chromatography to give the title compound (0.042g).  
TLC: DCM/MeOH 90/10 (Rf=0.28).

**Intermediate 28**

**(11S,21R)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-6-O-methyl-12,11-[oxycarbonyl-(2-(4-(pyridin-3-yl)-imidazol-1-yl)acetamidomethyl)-methylene]-erythromycin A**

To a solution of 3-(1H-imidazol-4-yl)-pyridine (0.005g) in anhydrous DMF (2mL) cooled to 0°C sodium hydride (0.001g) was added under nitrogen atmosphere. The reaction mixture was stirred at 0°C for 1h then a solution of intermediate 14 (0.030g) in anhydrous DMF (1mL) was added. After 16h at room temperature the reaction was quenched with water (5mL) and the mixture extracted with DCM (10mL). The organic phase was dried over

Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure and the crude material purified by preparative TLC (eluting with: DCM\MeOH 90\10) to give the title compound (0.020g).  
TLC: DCM\MeOH 90\10 (R<sub>f</sub>=0.35).

5 **Intermediate 29**

**(11S,21R)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-6-O-methyl-12,11-[oxycarbonyl-(1-(pyrrolidin-2-one)-methyl)-methylene]-erythromycin A**

To a solution of intermediate 15 (0.095g) in anhydrous DMF (8mL) cooled to 0°C, sodium hydride (0.004g) was added under nitrogen atmosphere. The mixture was stirred at 0°C for 1h and at room temperature for 18h. Water (5mL) was added and extracted with a mixture Et<sub>2</sub>O\DCM 80\20 (3x10mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure and the crude material purified by flash chromatography (eluting with: DCM\MeOH 90\10) to give the title compound (0.050g).  
m/z ([MH]<sup>+</sup>) = 753.

15

**Intermediate 30**

**(11S,21R)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-6-O-methyl-12,11-[oxycarbonyl-(2-(quinoxalin-2-ylsulfanyl)-acetamidomethyl)-methylene]-erythromycin A**

To a solution of intermediate 13 (0.075g) in anhydrous DMF (7mL) (quinoxalin-2-ylsulfanyl)-acetic acid (0.029g), HATU (0.046g) and DIPEA (0.030mL) were sequentially added under nitrogen atmosphere. The mixture was stirred at room temperature for 6h. The solvent was evaporated under reduced pressure and the residue dissolved in DCM (20mL). The organic phase was washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x15mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM\MeOH 90\10) to give the title compound (0.069g).  
m/z ([MH]<sup>+</sup>) = 887.

25

**Intermediate 31**

**(11S,21R)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-6-O-methyl-12,11-[oxycarbonyl-(3-(quinoxalin-2-ylsulfanyl)-propionamidomethyl)-methylene]-erythromycin A**

To a solution of intermediate 13 (0.030g) in anhydrous DMF (3mL) 3-(quinoxalin-2-ylsulfanyl)-propionic acid (0.012g), HATU (0.018g) and DIPEA (0.012mL) were sequentially added under nitrogen atmosphere. The mixture was stirred at room temperature for 6h then the solvent was evaporated under reduced pressure. The residue was dissolved in DCM (15mL), the organic phase washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x10mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM\MeOH 90\10) to give the title compound (0.035g).  
m/z ([MH]<sup>+</sup>) = 901.

35

**Intermediate 32****(11*S*,21*R*)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-6-O-methyl-12,11-[oxycarbonyl-[(quinolin-4-ylmethylene)-amino]-methyl)-methylene]-erythromycin A**

- 5 A solution of intermediate 13 (0.090g) and quinoline-4-carbaldehyde (0.023g) in anhydrous toluene (5mL) was heated at 50°C for 8h under nitrogen atmosphere. Solvent evaporation under reduced pressure gave the title compound (0.100g).  
m/z ([MH]<sup>+</sup>) = 824.

10 **Intermediate 33**

**2',4''-O-Diacetyl-6-O-allyl-erythromycin**

- To a solution of 6-OAllyl erythromycin A (1g) in anhydrous DCM (5mL) cooled to 0°C, TEA (0.5mL), DMAP (0.008g) and acetic anhydride (0.31mL) were added under nitrogen atmosphere. The resulting mixture was stirred at 0°C for 1h and overnight at room temperature. Then a saturated NH<sub>4</sub>Cl aqueous solution (30mL) was added the mixture extracted with DCM (2x50mL). The aqueous phase was neutralised with a saturated NaHCO<sub>3</sub> aqueous solution and extracted again with DCM (2x50mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure to give the title compound (1g).  
20 m/z ([MH]<sup>+</sup>) = 858.

**Intermediate 34****11,12-Carbonate-2',4''-O-diacetyl-11,12-dideoxy-6-O-allyl-erythromycin**

- To a solution of intermediate 33 (4.13g) in anhydrous DCM (85mL), pyridine (0.8mL) and then phosgene (20% sol in toluene, 2.55mL) were added at 0°C under nitrogen atmosphere. The resulting mixture was stirred at 0°C for 30min and then at room temperature for 1h. The reaction mixture was then diluted with water (150mL) and extracted with DCM (2x200mL). The organic layer was washed with water (3x100mL), dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure to give the title compound (4.02g).  
30 m/z ([MH]<sup>+</sup>) = 884.

**Intermediate 35****11-Deoxy-2',4''-O-diacetyl-10,11-didehydro-6-O-allyl-erythromycin**

- To a solution of intermediate 34 (4.02g) in toluene (45mL) and EtOAc (23mL), DBU (0.71mL) was added at room temperature. The resulting mixture was heated to 85°C for 6h. The mixture was then diluted with brine (100mL), extracted with EtOAc (2x200mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. Solvent evaporation under reduced pressure and purification by flash chromatography of the crude material (eluting with: DCM/MeOH/NH<sub>4</sub>OH 95/4/0.01) gave the title compound (1.70g).  
40 m/z ([MH]<sup>+</sup>) = 840.

**Intermediate 36**

**12-Chloroethanoyl-11-deoxy-2',4''-O-diacetyl-10,11-didehydro-6-O-allyl-erythromycin****4**

To a solution of intermediate **35** (1.7g) in anhydrous DCM (50mL) cooled at 0°C, pyridine (0.66mL), DMAP (0.012g) and chloroacetic anhydride (0.695g) were added under nitrogen atmosphere. The resulting mixture was stirred for 30min at 0°C and then at room temperature for 2.5h. The mixture was diluted with water (50mL), neutralised with a saturated aqueous solution of NaHCO<sub>3</sub> and extracted with DCM (2x100mL). The organic phase was washed with water (3x75mL), dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure to give the title compound (1.8g).

m/z ([MH]<sup>+</sup>) = 916.

**Intermediate 37****2'-O-Acetyl-12-chloroethanoyl-3-decladinosyl-11-deoxy-10,11-didehydro-6-O-allyl-erythromycin 4**

To a solution of intermediate **36** (1.8g) in THF (35mL), a 6N HCl aqueous solution (10mL) was added at 0°C. The resulting mixture was stirred overnight at room temperature, then it was diluted with water (50mL). The pH of the solution was brought to 8-9 by addition of solid NaHCO<sub>3</sub> and a 1% NaOH aqueous solution, then the aqueous phase was extracted with DCM (2x100mL). Solvent evaporation under reduced pressure and treatment of the residue with Et<sub>2</sub>O gave the title compound (1.4g).

m/z ([MH]<sup>+</sup>) = 716.

**Intermediate 38****(11S,21R)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-6-O-allyl-12,11-[oxycarbonyl-(cyano)-methylene]-erythromycin 4**

To a solution of intermediate **37** (1.3g) in anhydrous DMF (40mL) potassium cyanide (0.500g) was added under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1h, quenched with a 5% NaHCO<sub>3</sub> aqueous solution (50mL) and extracted with DCM (2x50mL). The crude material was purified by flash chromatography (eluting with: DCM/MeOH/NH<sub>4</sub>OH 95/4/0.01) to give the title compound (0.42g).

m/z ([MH]<sup>+</sup>) = 707.

**Intermediate 39****2'-O-Acetyl-12-azidoethanoyl-3-decladinosyl-11-deoxy-10,11-didehydro-6-O-allyl-erythromycin A**

To a solution of intermediate **37** (1.42g) in anhydrous DMF (110mL), sodium azide (0.211g) was added under nitrogen atmosphere. The mixture was heated to 80°C for 10min then quenched with water (100mL) and extracted with EtOAc (3x200mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give the title compound (1.36g).

m/z ([MH]<sup>+</sup>) = 723.

**Intermediate 40****2'-O-Acetyl-12-aminoethanoyl-3-decladinosyl-11-deoxy-10,11-didehydro-6-O-allyl-erythromycin A**

To a solution of intermediate 39 (1.36g) in THF (25mL), triphenylphosphine (0.985g) and water (0.034mL) were added. The mixture was stirred at room temperature overnight. After evaporating the solvent, the residue was dissolved in DCM (100mL) and the solution washed with water (2x100). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum to give the title compound (1.30g).

m/z ([MH]<sup>+</sup>) = 697.

**Intermediate 41****2'-O-Acetyl-12-(benzhydrylidene)-aminoethanoyl-3-decladinosyl-11-deoxy-10,11-didehydro-6-O-allyl-erythromycin A**

A solution of intermediate 40 (1.30g) and benzophenone imine (0.9mL) in anhydrous DCM (15mL) was stirred at room temperature under nitrogen atmosphere. After 30h the reaction was quenched with water (50mL) and extracted with DCM (3x100mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give the title compound (1.60g).

m/z ([MH]<sup>+</sup>) = 861.

**Intermediate 42****(11S,21R,S)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-6-O-allyl-12,11-oxycarbonyl-(benzhydrylideneamino)-methylenel-erythromycin A**

A solution of intermediate 41 (1.60g) and DBU (0.3mL) in acetonitrile (90mL) and water (9mL) was stirred at room temperature for 2h. Then the solvents were evaporated and the crude material was dissolved in DCM (100mL). The mixture was washed with water (2x100mL), the organic phase dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH/NH<sub>3</sub> 9.5\0.4\0.03) to give the title compound (0.528g).

m/z ([MH]<sup>+</sup>) = 861.

**Intermediate 43****Methyl (4-pyridin-3-yl-1H-imidazol-1-yl)acetate**

To a stirred suspension of sodium hydride (0.769g) in anhydrous DMF (30mL) under nitrogen atmosphere, a solution of 3-(1H-imidazol-4-yl)-pyridine (3g) in anhydrous DMF (10mL) was added dropwise at room temperature. The mixture was stirred for 30min then methyl bromoacetate (2.4mL) was added dropwise. After stirring for 2h the solvent was evaporated under reduced pressure, the residue diluted with EtOAc (200mL) and washed with water (50mL). The aqueous phase was further extracted with EtOAc (2x40mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure and the crude material purified by flash chromatography (eluting with: DCM/MeOH 95\5) to give the title compound (2.78g).

$m/z$  ( $[MH]^+$ ) = 218.

**Intermediate 44**

**Methyl 3-(4-pyridin-3-yl-1H-imidazol-1-yl)-propionate**

- 5 To a stirred suspension of sodium hydride (0.165g) in anhydrous DMF (2.5mL) cooled at 0°C a solution of 3-(1H-imidazol-4-yl)-pyridine (1g) in anhydrous DMF (5mL) was added dropwise under nitrogen atmosphere. The mixture was stirred for 15min at room temperature then a solution of methyl 3-bromopropanoate (0.830mL) in anhydrous DMF (5mL) was added dropwise. After stirring for 2h at 70°C the solvent was evaporated under reduced pressure, the residue diluted with EtOAc (50mL) and washed with water (15mL). The aqueous phase was further extracted with EtOAc (3x15mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure and the crude product was purified by flash chromatography (eluting with: DCM/MeOH from 95/5 to 90/10) to give the title compound (0.530g).
- 10  $m/z$  ( $[MH]^+$ ) = 232.

**Intermediate 45**

**Methyl 4-(4-pyridin-3-yl-1H-imidazol-1-yl)butyrate**

- 20 To a stirred suspension of sodium hydride (0.745g) in anhydrous DMF (8mL) cooled at 0°C a solution of 3-(1H-imidazol-4-yl)-pyridine (3g) in anhydrous DMF (16mL) was added dropwise under nitrogen atmosphere. The mixture was stirred for 15min at room temperature then a solution of methyl 4-chloro-butanoate (2.76mL) in anhydrous DMF (16mL) was added dropwise. After stirring for 2.5h at 70°C the solvent was evaporated under reduced pressure, the residue diluted with EtOAc (150mL) and washed with water (50mL). The aqueous phase was further extracted with EtOAc (3x40mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure and the crude product was purified by flash chromatography (eluting with: DCM/MeOH 96/4) to give the title compound (2.2g).
- 25  $m/z$  ( $[MH]^+$ ) = 246.

30 **Intermediate 46**

**Methyl 5-(4-pyridin-3-yl-1H-imidazol-1-yl)pentanoate**

- 35 To a stirred suspension of sodium hydride (0.745g) in anhydrous DMF (8mL) cooled at 0°C a solution of 3-(1H-imidazol-4-yl)-pyridine (3g) in anhydrous DMF (16mL) was added dropwise under nitrogen atmosphere. The mixture was stirred for 15min at room temperature then a solution of methyl 5-bromo-pentanoate (3.55mL) in anhydrous DMF (16mL) was added dropwise. After stirring for 2h at 70°C the solvent was evaporated under reduced pressure, the residue diluted with EtOAc (150mL) and washed with water (50mL). The aqueous phase was further extracted with EtOAc (3x40mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure and the crude product was purified by flash chromatography (eluting with: DCM/MeOH 96/4) to give the title compound (4.25g).
- 40  $m/z$  ( $[MH]^+$ ) = 260.



**Intermediate 47****Sodium (4-Pyridin-3-yl-imidazol-1-yl)-acetate**

To a solution of intermediate **43** (0.100g) in acetone (2mL) at room temperature 1M NaOH aqueous solution (0.46mL) was added. The mixture was stirred at room temperature for 20h then to reflux for 8h. Solvent evaporation under reduced pressure gave the title compound (0.100g).

$m/z$  ( $[MH]^+$ ) = 204.

**Intermediate 48****Sodium 3-(4-Pyridin-3-yl-imidazol-1-yl)-propionate**

To a solution of intermediate **44** (0.100g) in acetone (1mL) at room temperature 1M NaOH aqueous solution (0.43mL) was added. The mixture was stirred at room temperature for 6h. Solvent evaporation under reduced pressure gave the title compound (0.099g).

$m/z$  ( $[MH]^+$ ) = 218.

**Intermediate 49****Sodium 4-(4-Pyridin-3-yl-imidazol-1-yl)-butyrate**

To a solution of intermediate **45** (0.100g) in acetone (1mL) at room temperature 1M NaOH aqueous solution (0.40mL) was added. The mixture was stirred at room temperature for 6 h. Solvent evaporation under reduced pressure gave the title compound (0.096g).

$m/z$  ( $[MH]^+$ ) = 232.

**Intermediate 50****Sodium 5-(4-Pyridin-3-yl-imidazol-1-yl)-pentanoate**

To a solution of intermediate **46** (0.100g) in acetone (1mL) at room temperature 1M NaOH aqueous solution (0.38mL) was added. The mixture was stirred at room temperature for 3 h. Solvent evaporation under reduced pressure gave the title compound (0.095g).

$m/z$  ( $[MH]^+$ ) = 246.

**Intermediate 51****1-Methoxy-2-(4-pyridin-3-yl-1H-imidazol-1-yl)ethanol**

To a stirred suspension of sodium hydride (0.166g) in anhydrous DMF (3mL) cooled to 0°C a solution of 3-(1H-imidazol-4-yl)-pyridine (1g) in anhydrous DMF (5mL) was added dropwise under nitrogen atmosphere. The reaction mixture was allowed to reach room temperature and after 15min a solution of bromoacetaldehyde dimethyl acetal (0.816mL) in anhydrous DMF (5mL) was added dropwise. The reaction mixture was stirred at 70°C for 4h and at room temperature overnight. After evaporating the solvent under reduced pressure the crude material was purified by flash chromatography (eluting with DCM/MeOH 90/10) to give the title compound (1.15g).

$m/z$  ( $[MH]^+$ ) = 234

TLC: DCM/MeOH 90/10 ( $R_f$ =0.5).

**Intermediate 52****3-(4-Pyridin-3-yl-1H-imidazol-1-yl)propionaldehyde**

To a solution of 3-(1H-imidazol-4-yl)-pyridine (0.350g) in anhydrous THF (15mL) cooled at 0°C acrylaldehyde (0.540mL) was added dropwise. The resulting solution was stirred at room temperature for 3 days. Solvent evaporation under reduced pressure gave the title compound (0.460g).

$m/z$  ( $[MH]^+$ ) = 202.

**Intermediate 53****4-(4-Pyridin-3-yl-1H-imidazol-1-yl)butan-1-ol**

To a solution of intermediate **45** (1.2g) in anhydrous THF (20mL) cooled at 0°C lithium aluminum hydride (1M in THF, 2.55mL) was added dropwise under nitrogen atmosphere. The reaction mixture was stirred for 2h at room temperature, then water (30mL) and EtOAc (75mL) were added. The solvents were evaporated under reduced pressure and the residue extracted with EtOAc (2x75mL). The combined organic layers were washed with a saturated sodium/potassium tartrate aqueous solution (80mL), dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH 95/5) to give the title compound (0.600g)

$m/z$  ( $[MH]^+$ ) = 218.

**Intermediate 54****4-(4-Pyridin-3-yl-1H-imidazol-1-yl)butyraldehyde**

To a solution of oxalyl chloride (0.225mL) in anhydrous DCM (7mL) cooled to -78°C under nitrogen atmosphere a solution of DMSO (0.275mL) in anhydrous DCM (2mL) was slowly added. After 15 min at -78°C a solution of intermediate **53** (0.280g) in anhydrous DCM (5mL) was dropped within 30min. The mixture was stirred at -40°C for 4h then TEA(0.900mL) was added. The reaction was allowed to reach room temperature then water (10mL) was added. The mixture was extracted with DCM (3x20mL), the organic phase dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure and the crude material purified by flash chromatography (eluting with: DCM/MeOH 90/10) to give the title compound (0.052g)

$m/z$  ( $[MH]^+$ ) = 216.

**Intermediate 55****5-(4-Pyridin-3-yl-1H-imidazol-1-yl)pentan-1-ol**

To a solution of intermediate **46** (3.54g) in anhydrous THF (40mL) cooled to 0°C, lithium aluminum hydride (1M in THF, 7.8mL) was added dropwise under nitrogen atmosphere. The reaction mixture was stirred for 2.5h at room temperature then water (50mL), EtOAc (100mL) and a 28% NH<sub>4</sub>OH aqueous solution until pH=9 were added. The solvents were evaporated under reduced pressure and the residue dissolved in EtOAc (2x100mL). The solution was washed with a saturated sodium/potassium tartrate aqueous solution, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure and the crude material purified by flash

chromatography (eluting with: DCM\MeOH from 95\5 to 90\10) to give the title compound (2.32g)

TLC: DCM\MeOH 95\5 (R<sub>f</sub>=0.18)

5 **Intermediate 56**

**5-(4-Pyridin-3-yl-1H-imidazol-1-yl)pentanal**

To a solution of oxalyl chloride (0.755mL) in anhydrous DCM (25mL) cooled to -78°C under nitrogen atmosphere, a solution of DMSO (1.23mL) in anhydrous DCM (8mL) was slowly added. After 15min at -78°C a solution of intermediate **55** (1g) in anhydrous DCM (18mL) was added dropwise over 30min. The mixture was stirred at -40°C for 3.5h then TEA(3.6mL) was added. The reaction mixture was allowed to reach room temperature then water (50mL) was added. The mixture was extracted with DCM (3x100mL), the organic phase dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure and the crude material purified by flash chromatography (eluting with: DCM\MeOH 92\8) to give the title compound (0.635g)

15 m/z ([MH]<sup>+</sup>) = 230.

**Intermediate 57**

**4-[(E,Z)-2-Methoxyvinyl]quinoline**

To a solution of (methoxymethyl)triphenylphosphonium chloride (3.27g) in anhydrous THF (60mL) cooled to -78°C sodium bis(trimethylsilyl)amide (1M in THF, 9.5mL) was added under nitrogen atmosphere and the solution was stirred for 15min. A solution of 4-quinoline carboxaldehyde (1g) in anhydrous THF (10mL) was added and the reaction mixture was stirred at -78°C for 30min, at 0°C for 1.5h, then at room temperature overnight. The reaction was quenched with water (50mL) and extracted with EtOAc (75mL). The aqueous phase was neutralised with a saturated NH<sub>4</sub>Cl (50ml) aqueous solution and extracted again with EtOAc (2x75mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure and the crude material purified by flash chromatography (eluting with: Hexane\EtOAc from 60\40 to 50\50) to give the title compound (0.905g).

25 m/z ([MH]<sup>+</sup>) = 186.

30

**Intermediate 58**

**4-[3-(1,3-Dioxolan-2-yl)propyl]quinoline**

To a solution of [2-(1,3-dioxolan-2-yl)-ethyl]-triphenylphosphonium bromide (10.6g) in anhydrous THF (150mL) cooled to -78°C a solution of sodium bis(trimethylsilyl)amide (1M in THF, 23.9mL) was added dropwise under nitrogen atmosphere. The mixture was stirred at -78°C for 30min then a solution of 4-quinoline carboxaldehyde (2.5g) in anhydrous THF (30mL) was added. The mixture was allowed to reach room temperature, DBU (1.8mL) was added and the mixture stirred for 6h at 50°C. The reaction was quenched with a saturated NH<sub>4</sub>Cl aqueous solution of (100mL) and extracted with EtOAc (3x150mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure and the crude material filtered on a silica pad (eluting with: cyclohexane\EtOAc 70\30). After evaporating the solvent under reduced pressure, the residue was dissolved in MeOH (20mL), palladium

35

40

(10wt. % on carbon powder, 0.360g) was added and the mixture stirred under hydrogen atmosphere (1.5 atm) for 2h. The mixture was filtered over a celite pad eluting with MeOH (2x100mL) and purification by flash chromatography (eluting with: Et<sub>2</sub>O) gave the title compound (0.700g).

5 m/z ([MH]<sup>+</sup>) = 244.

#### **Intermediate 59**

##### **4-Quinolin-4-yl-butyraldehyde**

10 To a solution of intermediate **58** (0.500g) in acetone (5mL) a 2N HCl aqueous solution (5mL) was added and the mixture stirred at 50°C for 2h. After evaporation of the solvent under reduced pressure, NH<sub>4</sub>OH was added to the residue until pH=9. Aqueous solution was extracted with DCM (2x35mL), the organic phase dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: EtOAc\cyclohexane 80\20) to give the title compound (0.315g).

15 m/z ([MH]<sup>+</sup>) = 200.

#### **Intermediate 60**

##### **4-Quinolin-4-yl-butyric acid**

20 To a solution of intermediate **59** (0.160g) in acetone (4mL) potassium permanganate (0.063g) was added portionwise within 1h. After solvent evaporation, water (4mL) was added and the mixture refluxed for 30min. The reaction mixture was slowly cooled to 0°C and kept at 0°C overnight. The reaction mixture was filtered through a celite pad eluting with DCM (5mL) and after removing the solvent under vacuum the crude product was purified by flash chromatography (eluting with: DCM\MeOH 90\10) to give the title compound (0.050g).

25 m/z ([MH]<sup>+</sup>) = 216.

#### **Intermediate 61**

##### **Ethyl 5-quinolin-4-yl-pentanoate**

30 To a stirred suspension of [3-(ethoxycarbonyl)-propyl]-triphenylphosphonium bromide (5.6g) in anhydrous THF (100mL) cooled to -78°C a solution of sodium bis(trimethylsilyl)amide (1M in THF, 12mL) was added dropwise under nitrogen atmosphere. The mixture was stirred at -78°C for 1h then a solution of 4-quinoline carboxaldehyde (1.6g) in anhydrous THF (15mL) was dropped. The mixture was allowed to reach room temperature, stirred for 2h then heated to 50°C and stirred for 4h. The reaction was quenched with a saturated NH<sub>4</sub>Cl aqueous solution (50mL) and extracted with EtOAc (3x100mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure and the crude material purified by filtration on a silica gel pad (eluting with: cyclohexane\EtOAc 70\30). After evaporating the solvent under reduced pressure, the residue was dissolved in MeOH (10mL), palladium (10wt. % on carbon powder, 0.060g) was added and the mixture stirred under hydrogen atmosphere (1.5 atm) for 1h. The mixture was filtered through a celite pad eluting with MeOH (2x50mL) and subsequent solvent evaporation under reduced pressure gave the title compound (0.860g).

40 m/z ([MH]<sup>+</sup>) = 258.

**Intermediate 62****5-Quinolin-4-yl-pentanoic acid**

To a solution of intermediate **61** (0.194g) in acetone (1mL) at room temperature 1M NaOH aqueous solution (0.78mL) was added. The mixture was refluxed for 2h. Solvent evaporation under reduced pressure gave the title compound (0.181g).  
 $m/z$  ( $[MH]^+$ ) = 230.

**Intermediate 63****5-Quinolin-4-yl-pentanal**

To a solution of intermediate **61** (0.050g) in anhydrous toluene (1mL) cooled to  $-78^\circ\text{C}$ , diisobutylaluminium hydride (1M sol. in toluene, 0.39mL) was slowly added. The reaction mixture was stirred for 1h at  $-78^\circ\text{C}$ , then quenched with 2mL of a mixture of water (0.25mL), acetic acid (1mL) and  $\text{Et}_2\text{O}$  (3mL) at  $-78^\circ\text{C}$ . The temperature was allowed to reach room temperature then the crude material was filtered through a celite pad eluting with DCM (3x10mL). The organic phase was dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to give the title compound (0.040g).  
 $m/z$  ( $[MH]^+$ ) = 214.

**Intermediate 64****Methyl 3-(4-phenyl-1H-imidazol-1-yl)propionate**

To a stirred suspension of sodium hydride (0.017g) in anhydrous DMF (0.250mL) cooled at  $0^\circ\text{C}$  a solution of 4-phenyl-1H-imidazole (0.100g) in anhydrous DMF (0.8mL) was added dropwise under nitrogen atmosphere. The mixture was stirred for 15min at room temperature then a solution of 3-bromo-propionic acid methyl ester (0.083mL) in anhydrous DMF (0.3mL) was added dropwise. After stirring for 2h at  $70^\circ\text{C}$  the solvent was evaporated under reduced pressure, the residue diluted with EtOAc (5mL) and washed with water (3mL). The aqueous phase was further extracted with EtOAc (3x5mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , concentrated under reduced pressure and the crude material was purified by flash chromatography (eluting with: DCM/MeOH from 100/0 to 95/5) to give the title compound (0.128g).  
 $m/z$  ( $[MH]^+$ ) = 231.

**Intermediate 65****Sodium 3-(4-Phenyl-imidazol-1-yl)-propionate**

To a solution of intermediate **64** (0.034g) in acetone (0.50mL) at room temperature a 1M NaOH aqueous solution (0.15mL) was added. The mixture was stirred at room temperature for 3h. Solvent evaporation under reduced pressure gave the title compound (0.035g).  
 $m/z$  ( $[MH]^+$ ) = 217.

**Intermediate 66****Methyl (4-phenyl-1H-imidazol-1-yl)acetate**

To a stirred suspension of sodium hydride (0.037g) in anhydrous DMF (0.550mL) cooled at 0°C a solution of 4-phenyl-1*H*-imidazole (0.200g) in anhydrous DMF (1.6mL) was added dropwise under nitrogen atmosphere. The mixture was stirred for 15min at room temperature then a solution of 2-chloro-acetic acid methyl ester (0.134mL) in anhydrous DMF (0.60mL) was added dropwise. After stirring for 2h at 70°C and overnight at room temperature the mixture was diluted with Et<sub>2</sub>O (25mL) and washed with water (10mL). The aqueous phase was further extracted with Et<sub>2</sub>O (3x15mL). The collected organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure and the crude product was purified by flash chromatography (eluting with: DCM\MeOH from 100\0 to 96\4) to give the title compound (0.210g).  
m/z ([MH]<sup>+</sup>) = 217.

#### **Intermediate 67**

##### **Sodium 3-(4-Phenyl-imidazol-1-yl)-propionate**

To a solution of intermediate 66 (0.190g) in acetone (2.5mL) at room temperature, a 1.2M NaOH aqueous solution (0.730mL) was added. The mixture was stirred at room temperature for 2.5h and then solvent evaporation under reduced pressure gave the title compound (0.205g).  
m/z ([MH]<sup>+</sup>) = 203

#### **Intermediate 68**

##### **Methyl 3-(4-thien-2-yl-1*H*-imidazol-1-yl)propionate**

To a stirred suspension of sodium hydride (0.013g) in anhydrous DMF (0.250mL) cooled at 0°C a solution of 4-thiophen-2-yl-1*H*-imidazole (0.100g) in anhydrous DMF (1.6mL) was added dropwise under nitrogen atmosphere. The mixture was stirred for 15min at room temperature then a solution of methyl 3-bromopropionate (0.100mL) in anhydrous DMF (0.3mL) was added dropwise. After stirring for 5h at 70°C and overnight at room temperature the solvent was evaporated under reduced pressure, the residue dissolved with EtOAc (5mL) and the solution washed with water (3mL). The aqueous phase was further extracted with EtOAc (3x5mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure and the crude material was purified by flash chromatography (eluting with: DCM\MeOH from 100\0 to 95\5) to give the title compound (0.013g).  
m/z ([MH]<sup>+</sup>) = 237.

#### **Intermediate 69**

##### **Sodium 3-(4-thien-2-yl-1*H*-imidazol-1-yl)propionate**

To a solution of intermediate 68 (0.013g) in acetone (0.3mL) at room temperature, a 1M NaOH aqueous solution (0.055mL) was added. The mixture was stirred at room temperature for 5h and then solvent evaporation under reduced pressure gave the title compound (0.012g).  
m/z ([MH]<sup>+</sup>) = 223.

#### **Intermediate 70**

**Sodium 3-(3-thiazol-2-yl-pyrazol-1-yl)-propionate**

To a stirred suspension of sodium hydride (0.016g) in anhydrous DMF (0.3mL) cooled at 0°C a solution of 2-(1*H*-pyrazol-3-yl)-thiazole (0.100g) in anhydrous DMF (0.8mL) was added dropwise under nitrogen atmosphere. The mixture was stirred for 15min at room temperature then a solution of 3-bromo-propionic acid methyl ester (0.080mL) in anhydrous DMF (0.3mL) was added dropwise. After stirring for 4h at 70°C the solvent was evaporated under reduced pressure, the residue diluted with EtOAc (5mL) and washed with water (3mL). The aqueous phase was further extracted with EtOAc (3x5mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was dissolved in acetone (1mL) and a 1.2N NaOH aqueous solution (0.55mL) was added. The mixture was stirred at room temperature overnight. Solvent evaporation under reduced pressure gave the title compound (0.025g).  
m/z ([MH]<sup>+</sup>) = 224.

**Intermediate 71****Ethyl [(3-methoxyquinoxalin-2-yl)thio]acetate**

To a solution of 2-chloro-3-methoxy-quinoxaline (0.100g) in anhydrous DMF (3mL) potassium carbonate (0.142g) and mercapto-acetic acid ethyl ester (0.084mL) were added and the resulting mixture was stirred at 80°C for 1.5h. The solvent was removed under reduced pressure, water (5mL) was added and the mixture was extracted with EtOAc (3x10mL). The combined organic phases were washed with brine (5mL), dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure. The crude material was purified by flash chromatography (eluting with: cyclohexane/EtOAc 80/20) to afford the title compound (0.065g).  
m/z ([MH]<sup>+</sup>) = 255  
TLC: cyclohexane/EtOAc 80/20 (R<sub>f</sub>=0.57).

**Intermediate 72****[(3-Methoxyquinoxalin-2-yl)thio]acetic acid**

To a solution of intermediate **71** (0.060g) in THF (2mL) a 3N NaOH aqueous solution (2mL) was added. The mixture was vigorously stirred at room temperature overnight, then after solvent evaporation, a 1N HCl aqueous solution was added until pH=1. The solution was extracted with DCM (3x8mL), the organic phase was washed with brine (5mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give the title compound (0.045g).  
m/z ([MH]<sup>+</sup>) = 227  
TLC: EtOAc/MeOH 98/2 (R<sub>f</sub>=0.48)

**Intermediate 73****Ethyl (quinoxalin-2-yloxy)acetate**

To a solution of quinoxalin-2-ol (2g) in acetone (30mL) potassium carbonate (3.8g) and chloroacetic acid ethyl ester (2.2mL) were added and the resulting mixture was stirred at reflux for 6h. After evaporating the solvent under reduced pressure, water (30mL) was added and the mixture extracted with EtOAc (3x50mL). The organic phase was washed with brine

(30mL) dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure. The crude material was purified by flash chromatography (eluting with: cyclohexane/EtOAc 3/2) to afford the title compound (1.5g).

m/z ([MH]<sup>+</sup>) = 233.

5

#### **Intermediate 74**

##### **(Quinoxalin-2-yl-oxy)acetic acid**

To a solution of intermediate **73** (0.300g) in THF (10mL) a 3N NaOH aqueous solution (10mL) was added. The mixture was vigorously stirred at room temperature for 1h, then after evaporation of the solvent, a 1N HCl aqueous solution was added until pH=1. The aqueous solution was extracted with DCM (3x20mL), the organic phase was washed with brine (10mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give the title compound (0.230g).

10

m/z ([MH]<sup>+</sup>) = 205

15

#### **Intermediate 75**

##### **3-[4-(3,5-Difluorophenyl)-1H-pyrazol-1-yl]propionaldehyde**

To a solution of 4-(3,5-difluoro-phenyl)-1H-pyrazole (0.050g) in anhydrous acetonitrile (2mL), acrylaldehyde (0.050mL) was added portionwise. The resulting solution was stirred at 55°C for 16h and then the solvent was removed under reduced pressure to give the title compound (0.52g).

20

m/z ([MH]<sup>+</sup>) = 237

#### **Intermediate 76**

##### **3-[4-(4-Chlorophenyl)-2,5-dimethyl-1H-imidazol-1-yl]propionaldehyde**

To a solution of 4-(4-chloro-phenyl)-2,5-dimethyl-1H-imidazole (0.030g) in anhydrous acetonitrile (3mL), acrylaldehyde (0.069mL) was added portionwise. The resulting solution was stirred at 50°C for 24h and then the solvent was removed under reduced pressure to give the title compound (0.036g).

25

m/z ([MH]<sup>+</sup>) = 263

30

#### **Intermediate 77**

##### **3-[4-(4-Nitrophenyl)-1H-imidazol-1-yl]propionaldehyde**

To a solution of 4-(4-nitro-phenyl)1H-imidazole (0.100g) in anhydrous acetonitrile (12mL), acrylaldehyde (0.450mL) was added portionwise. The resulting solution was stirred at 50°C for 5 days. Solvent was removed under reduced pressure to give the title compound (0.120g).

35

m/z ([MH]<sup>+</sup>) = 246

#### **Intermediate 78**

##### **3-(4-Pyridin-4-yl-imidazol-1-yl)-propionaldehyde**

To a solution of 4-(1H-imidazol-4-yl)-pyridine (0.040g) in anhydrous acetonitrile (2mL) acrylaldehyde (0.050mL) was added portionwise. The resulting solution was stirred at 55°C

40



for 8h and at room temperature overnight. Solvent was removed under reduced pressure to give the title compound (0.42g).

$m/z$  ( $[MH]^+$ ) = 202

5 **Intermediate 79**

**3-(3-Trifluoromethyl-1H-pyrazol-4-yl)-propionaldehyde**

To a solution of oxalyl chloride (0.127mL) in anhydrous DCM (4mL) cooled to  $-78^\circ\text{C}$  under nitrogen atmosphere DMSO (0.155mL) was slowly added. After stirring for 30min at  $-78^\circ\text{C}$  a solution of 3-(3-trifluoromethyl-1H-pyrazol-4-yl)-propan-1-ol (0.094mL) in anhydrous DCM (3mL) was added dropwise. The mixture was stirred at  $-40^\circ\text{C}$  for 3h then TEA(0.507mL) was added. The reaction was allowed to reach room temperature then a saturated  $\text{NaHCO}_3$  aqueous solution (10mL) was added and the mixture extracted with DCM (3x10mL). The organic phase was washed with brine (10mL), dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to give the title compound (0.100g)

15  $m/z$  ( $[MH]^+$ ) = 193

**Intermediate 80**

**3-[5-Methyl-4-(4-trifluoromethyl-phenyl)-1H-imidazol-1-yl]-propionaldehyde**

To a solution of 5-methyl-4-(4-trifluoromethyl-phenyl)-1H-imidazole (0.030g) in anhydrous acetonitrile (2mL) acrylaldehyde (0.027mL) was added. The resulting solution was stirred at  $50^\circ\text{C}$  for 24h and at room temperature for 12h. Solvent was removed under reduced pressure to give the title compound (0.038g).

$m/z$  ( $[MH]^+$ ) = 283

25 **Intermediate 81**

**3-Pyridin-3-yl-propionaldehyde**

To a solution of oxalyl chloride (0.127mL) in anhydrous DCM (4mL) cooled to  $-78^\circ\text{C}$  under nitrogen atmosphere DMSO (0.155mL) was slowly added. After 20min at  $-78^\circ\text{C}$  a solution 3-pyridin-3-yl-propan-1-ol (0.100g) in anhydrous DCM (3mL) was added dropwise within 30min. The mixture was stirred at  $-40^\circ\text{C}$  for 3h then TEA(0.507mL) was added. The reaction was allowed to reach room temperature then water (5mL) was added. The mixture was extracted with DCM (3x10mL), the organic phase dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH from 100/0 to 95/5) to give the title compound (0.052g)

35  $m/z$  ( $[MH]^+$ ) = 136

**Intermediate 82**

**3-(4-Pyridin-2-yl-pyrazol-1-yl)-propionaldehyde**

To a solution of 2-(1H-pyrazol-4-yl)-pyridine (0.058g) in anhydrous acetonitrile (2mL) acrylaldehyde (0.022mL) was added. The resulting solution was stirred at  $50^\circ\text{C}$  for 3h. Solvent was removed under reduced pressure to give the title compound (0.060g).

$m/z$  ( $[MH]^+$ ) = 202

**Intermediate 83****3-Pyridin-4-yl-propionaldehyde**

To a solution of oxalyl chloride (0.127mL) in anhydrous DCM (3mL) cooled to  $-70^{\circ}\text{C}$  under nitrogen atmosphere, a solution of DMSO (0.155mL) in anhydrous DCM (2mL) was added dropwise. The reaction mixture was stirred for 30min then a solution of 3-pyridin-4-yl-propan-1-ol (0.100g) in anhydrous DCM (2mL) was added dropwise in 30min. The mixture was stirred at  $-60^{\circ}\text{C}$  for 3h then the reaction mixture was allowed to reach  $-10^{\circ}\text{C}$  and TEA (0.507mL) was added. The reaction was stirred overnight reaching slowly the room temperature. A saturated  $\text{NaHCO}_3$  aqueous solution (5mL) was added, the organic phase was dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to give the title compound (0.100g).

$$m/z ([\text{MH}]^+) = 136$$

**Intermediate 84****3-(4-Pyrimidin-4-yl-pyrazol-1-yl)-propionaldehyde**

To a solution of 4-(1*H*-pyrazol-4-yl)-pyrimidine (0.022g) in anhydrous acetonitrile (2mL) acrylaldehyde (0.020mL) was added. The reaction mixture was stirred at  $50^{\circ}\text{C}$  for 1.5h. Solvent was removed under reduced pressure to give the title compound (0.025g).

$$m/z ([\text{MH}]^+) = 203$$

**Intermediate 85****3-(4-Pyridin-4-yl-pyrazol-1-yl)-propionaldehyde**

To a solution of 2-(1*H*-pyrazol-4-yl)-pyridine (0.050g) in anhydrous acetonitrile (2mL) acrylaldehyde (0.220mL) was added. The resulting solution was stirred at  $50^{\circ}\text{C}$  for 4h and at room temperature overnight. Solvent was removed under reduced pressure to give the title compound (0.050g).

$$m/z ([\text{MH}]^+) = 202$$

**Intermediate 86****3-[4-(3,5-Dichloro-phenyl)-2,5-dimethyl-imidazol-1-yl]-propionaldehyde**

To a solution of 4-(3,5-dichloro-phenyl)-2,5-dimethyl-1*H*-imidazole (0.035g) in anhydrous acetonitrile (3mL) acrylaldehyde (0.116mL) was added portionwise. The resulting solution was stirred at  $50^{\circ}\text{C}$  for 56h. Solvent was removed under reduced pressure to give the title compound (0.029g).

$$m/z ([\text{MH}]^+) = 297$$

**Intermediate 87****3-[2,5-Dimethyl-4-(3-trifluoromethyl-phenyl)-imidazol-1-yl]-propionaldehyde**

To a solution of 2,5-dimethyl-4-(3-trifluoromethyl-phenyl)-1*H*-imidazole (0.037g) in anhydrous acetonitrile (3mL) acrylaldehyde (0.120mL) was added portionwise. The resulting

solution was stirred at 50°C for 48h. Solvent was removed under reduced pressure to give the title compound (0.042g).

$m/z$  ( $[MH]^+$ ) = 297

5 **Intermediate 88**

**3-[4-(1,3-benzoxazol-2-yl)-1H-pyrazol-1-yl]-propionaldehyde**

To a stirred suspension of 2-(1H-pyrazol-4-yl)-1,3-benzoxazole (0.053g) in anhydrous acetonitrile (2mL) acrylaldehyde (0.220mL) was added. The reaction mixture was stirred at 50°C for 6h. After filtration the solvent was removed under reduced pressure to give the title compound (0.034g).

$m/z$  ( $[MH]^+$ ) = 242

**Intermediate 89**

**3-(5-Pyridin-4-yl-pyrazol-1-yl)-propionaldehyde**

15 To a solution of 4-(1H-pyrazol-3-yl)-pyridine (0.030g) in anhydrous acetonitrile (1mL) acrylaldehyde (0.085mL) was added. The reaction mixture was stirred at 50°C for 48h. Solvent was removed under reduced pressure to give the title compound (0.036g).

$m/z$  ( $[MH]^+$ ) = 202.

20 **Intermediate 90**

**3-(2-Pyridin-4-yl-imidazol-1-yl)-propionaldehyde**

To a solution of 4-(1H-imidazol-2-yl)-pyridine (0.050g) in anhydrous acetonitrile (3mL) acrylaldehyde (0.080mL) was added. The reaction mixture was stirred at 50°C for 14h. Solvent was removed under reduced pressure to give the title compound (0.050g).

25  $m/z$  ( $[MH]^+$ ) = 202

**Intermediate 91**

**3-(4-Quinolin-2-yl-1H-pyrazol-1-yl)-propionaldehyde**

30 To a solution of 2-(1H-pyrazol-4-yl)quinoline (0.050g) in anhydrous acetonitrile (5mL) acrylaldehyde (0.116mL) was added. The reaction mixture was stirred at 50°C for 3 days. Solvent was removed under reduced pressure to give the title compound (0.050g).

$m/z$  ( $[MH]^+$ ) = 252

**Intermediate 92**

35 **3-(4-Quinolin-4-yl-1H-pyrazol-1-yl)-propionaldehyde**

To a solution of 4-(1H-pyrazol-4-yl)quinoline (0.050g) in anhydrous acetonitrile (4mL) acrylaldehyde (0.260mL) was added. The reaction mixture was stirred at 50°C for 7 days. Solvent was removed under reduced pressure to give the title compound (0.050g).

$m/z$  ( $[MH]^+$ ) = 252

40

**Intermediate 93**

**3-(4-Quinoxalin-2-yl-1H-pyrazol-1-yl)-propionaldehyde**

To a solution of 2-(1*H*-pyrazol-4-yl)quinoxaline (0.050g) in anhydrous acetonitrile (4mL) acrylaldehyde (0.156mL) was added. The reaction mixture was stirred at 50°C for 3 days. Solvent was removed under reduced pressure to give the title compound (0.050g).

$m/z$  ( $[MH]^+$ ) = 253

5

#### **Intermediate 94**

##### **3-Thien-3-yl-propionaldehyde**

To a solution of oxalyl chloride (0.190mL) in anhydrous DCM (6mL) cooled to -78°C under nitrogen atmosphere a solution of DMSO (0.230mL) in anhydrous DCM (4mL) was slowly added. After stirring for 30min at -78°C a solution of 3-thien-3-ylpropan-1-ol (0.150g) in anhydrous DCM (4mL) was added dropwise. The mixture was stirred at -40°C for 3h then TEA(0.750mL) was added. The reaction was allowed to reach room temperature then a saturated NaHCO<sub>3</sub> aqueous solution (10mL) was added and the mixture extracted with DCM (3x10mL). The organic phase was washed with brine (10mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give the title compound (0.140g)

15

$m/z$  ( $[MH]^+$ ) = 141

#### **Intermediate 95**

##### **3-[5-(3-Methyl-pyrazin-2-yl)-pyrazol-1-yl]-propionaldehyde**

To a solution of 2-methyl-3-(2*H*-pyrazol-5-yl)-pyrazine (0.030g) in anhydrous acetonitrile (1mL) acrylaldehyde (0.065mL) was added. The reaction mixture was stirred at 50°C for 60h. Solvent was removed under reduced pressure to give the title compound (0.038g).

20

$m/z$  ( $[MH]^+$ ) = 217.

#### **Intermediate 96**

##### **3-[2-(Methylthio)-1*H*-benzimidazol-1-yl]-propionaldehyde**

To a solution of 2-(methylthio)-1*H*-benzimidazole (0.030g) in anhydrous acetonitrile (1mL) acrylaldehyde (0.080mL) was added. The reaction mixture was stirred at 50°C for 48h. Solvent was removed under reduced pressure to give the title compound (0.039g).

25

$m/z$  ( $[MH]^+$ ) = 221

30

#### **Intermediate 97**

##### **3-[3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl]-propionaldehyde**

To a stirred suspension of Dess-Martin periodinane (0.163g) in anhydrous DCM (4mL) 3-[3-(4-chlorophenyl)-1*H*-pyrazol-5-yl]propan-1-ol (0.050g) was added and the mixture was stirred at room temperature overnight. The reaction was quenched with a Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution (5% in a saturated NaHCO<sub>3</sub> aqueous solution, 3mL), stirred for 1h then extracted with DCM (10mL). The organic phase washed with brine (5mL), separated, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give the title compound (0.040g).

35

$m/z$  ( $[MH]^+$ ) = 235

40

#### **Intermediate 98**

**3-[6-(Methylthio)-7H-purin-7-yl]-propionaldehyde**

To a solution of 6-(methylthio)-7H-purine (0.032g) in anhydrous acetonitrile (3mL) acrylaldehyde (0.040mL) was added. The reaction mixture was stirred at 80°C for 8h and overnight at room temperature. Solvent was removed under reduced pressure to give the title compound (0.042g).

$m/z$  ( $[MH]^+$ ) = 223

**Intermediate 99****3-(6-Methoxy-7H-purin-7-yl)-propionaldehyde**

To a solution of 6-methoxy-7H-purine (0.040g) in anhydrous acetonitrile (3mL) acrylaldehyde (0.057mL) was added. The reaction mixture was stirred at 80°C for 8h. Solvent was removed under reduced pressure to give the title compound (0.055g).

$m/z$  ( $[MH]^+$ ) = 207

**Intermediate 100****3-(6-Methoxy-2-oxo-1,3-benzoxazol-3(2H)-yl)-propionaldehyde**

To a solution of 6-methoxy-1,3-benzoxazol-2(3H)-one (0.072g) in anhydrous acetonitrile (2mL) was added acrylaldehyde (0.060mL). The reaction mixture was stirred at 50°C for 3h. Solvent was removed under reduced pressure to give the title compound (0.080g).

$m/z$  ( $[MH]^+$ ) = 222

**Intermediate 101****3-(1H-Pyrrolo[2,3-*b*]pyridin-1-yl)-propionaldehyde**

To a solution of 1H-pyrrolo[2,3-*b*]pyridine (0.040g) in anhydrous acetonitrile (3mL), acrylaldehyde (0.071mL) was added. The reaction mixture was stirred at 80°C for 6h and then the solvent was removed under reduced pressure to give the title compound (0.042g).

$m/z$  ( $[MH]^+$ ) = 175

**Intermediate 102****3-[3-(2,4-Dimethyl-1,3-thiazol-5-yl)-1H-pyrazol-1-yl]propionaldehyde**

To a solution of 2,4-dimethyl-5-(1H-pyrazol-3-yl)-1,3-thiazole (0.032g) in anhydrous acetonitrile (1mL) acrylaldehyde (0.040mL) was added. The reaction mixture was stirred at 50°C for 5h and then at room temperature for 3 days. Solvent evaporation under reduced pressure gave the title compound (0.042g).

$m/z$  ( $[MH]^+$ ) = 236

**Intermediate 103****3-(3H-Imidazo[4,5-*c*]pyridin-3-yl)propionaldehyde**

and

**3-(1H-Imidazo[4,5-*c*]pyridin-1-yl)propionaldehyde**

To a solution of 3H-imidazo[4,5-*c*]pyridine (0.050g) in anhydrous acetonitrile (4mL) acrylaldehyde (0.025mL) was added. The reaction mixture was stirred at 80°C overnight and

then solvent was removed under reduced pressure to give a 1\1 mixture of the title compounds (0.050g).

m/z ([MH]<sup>+</sup>) = 176

5 **Intermediate 104**

**3-(1H-Benzimidazol-1-yl) propionaldehyde**

To a solution of 1H-benzimidazole (0.050g) in anhydrous acetonitrile (4mL) acrylaldehyde (0.160mL) was added. The reaction mixture was stirred at 80°C overnight and then the solvent was removed under reduced pressure to give the title compound (0.050g).

10 m/z ([MH]<sup>+</sup>) = 175

**Intermediate 105**

**3-(3H-Imidazo[4,5-b]pyridin-3-yl)propionaldehyde**

15 To a solution of 3H-imidazo[4,5-b]pyridine (0.050g) in anhydrous acetonitrile (3mL) acrylaldehyde (0.250mL) was added. The reaction mixture was stirred at 80°C for 24h and then the solvent was removed under reduced pressure to give the title compound (0.050g).

m/z ([MH]<sup>+</sup>) = 176

**Intermediate 106**

20 **2-(3,3-Dimethoxy-propylsulfanyl)-quinoxaline**

To a solution of 2-quinoxalinethiol (0.200g) in a mixture of anhydrous dioxane\DMF 4\1 (5mL) sodium hydride (80% mineral oil, 0.044g) was added portionwise under a nitrogen atmosphere and the reaction mixture stirred at room temperature for 15min. Then 3-bromopropionaldehyde dimethyl acetal (0.200mL) was added and the solution was heated to 80°C for 1.5h. After dilution at room temperature with EtOAc (5mL), the solution was concentrated under reduced pressure, diluted with water (10mL) and extracted with EtOAc (3x10mL). The combined organic phases were then washed with brine (10mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under vacuum to give a crude material that was purified by flash chromatography (eluant: cyclohexane\EtOAc 3\1) to afford the title compound (0.280g).

30 m/z ([MH]<sup>+</sup>) = 265.

TLC: Cyclohexane\EtOAc 7\3 (R<sub>f</sub>=0.47).

**Intermediate 107**

**3-(4-Phenyl-1H-imidazol-1-yl)propionaldehyde**

35 To a solution of 4-phenyl-1H-imidazole (0.050g) in anhydrous acetonitrile (4mL) acrylaldehyde (0.210mL) was added. The reaction mixture was stirred at 80°C for 24h and then the solvent was removed under reduced pressure to give the title compound (0.050g).

m/z ([MH]<sup>+</sup>) = 201.

40 **Intermediate 108**

**4-[1-(2,2-Dimethoxyethyl)-1H-imidazol-4-yl]pyridine**

To a stirred suspension of sodium hydride (0.009g) in anhydrous DMF (0.5mL) 4-(1*H*-imidazol-4-yl)pyridine (0.040g) was added under nitrogen atmosphere and the reaction mixture was stirred at room temperature for 30min. Then 2-bromoacetaldehyde dimethyl acetal (0.040mL) was added and the solution was heated to 70°C for 8h. After cooling to room temperature the solvent was evaporated to give the title compound (0.064g)  
m/z ([MH]<sup>+</sup>)=234

#### **Intermediate 109**

##### **2-(2,2-Dimethoxy-ethylsulfanyl)-quinoxaline**

To a solution of 2-quinoxalinethiol (0.200g) in a mixture of anhydrous dioxane\DMF 4\1 (5mL) sodium hydride (80% mineral oil, 0.044g) was added portionwise under nitrogen atmosphere and the reaction mixture stirred at room temperature for 15min. Then 2-bromoacetaldehyde dimethyl acetal (0.175mL) was added and the solution was heated to 80°C for 4.5h. After dilution at room temperature with EtOAc (5mL), the solution was concentrated under reduced pressure, diluted with water (10mL) and extracted with EtOAc (3x10mL). The combined organic phases were washed with brine (10mL), dried over Na<sub>2</sub>SO<sub>4</sub>, evaporated under vacuum obtaining a crude product that was purified by flash chromatography (eluting with: Cyclohexane\EtOAc 3\1) afforded the title compound (0.167g).  
m/z ([MH]<sup>+</sup>) = 251.  
TLC: Cyclohexane\EtOAc 7\3 (R<sub>f</sub>=0.52).

#### **Intermediate 110**

##### **3-(4-(Thiophen-2-yl)-imidazol-1-yl)-propionaldehyde**

To a solution of 4-thiophen-2-yl-1*H*-imidazole (0.030g) in anhydrous acetonitrile (3mL) TEA(0.022mL) was added. After stirring at room temperature for 15min acrylaldehyde (0.034mL) was added dropwise and the resulting solution was heated to 75°C for 8h and then the solvent was removed under reduced pressure to give the title compound (0.033g).  
m/z ([MH]<sup>+</sup>) = 207.

#### **Intermediate 111**

##### **3-(6-Methyl-2-oxo-1,3-benzoxazol-3(2*H*)-yl)propanal**

To a solution of 6-methyl-1,3-benzoxazol-2(3*H*)-one (0.030g) in anhydrous acetonitrile (2mL) acrylaldehyde (0.060mL) was added. The reaction mixture was stirred at 50°C for 48h and then the solvent was removed under reduced pressure to give the title compound (0.040g).  
m/z ([MH]<sup>+</sup>) = 206.

#### **Intermediate 112**

##### **4-[1-(2,2-dimethoxyethyl)-1*H*-imidazol-2-yl]pyridine**

To a stirred suspension of sodium hydride (0.009g) in anhydrous DMF (0.5mL) 4-(1*H*-imidazol-2-yl)pyridine (0.040g) was added under nitrogen atmosphere and the reaction

mixture was stirred at room temperature for 30min. Then 2-bromoacetaldehyde dimethyl acetal (0.040mL) was added and the solution was heated to 70°C for 30h. After cooling to room temperature the solvent was evaporated under vacuum to give the title compound (0.064g)

5  $m/z$  ( $[MH]^+$ )=234

#### **Intermediate 113**

##### **3,4-Dimethyl-5-[1-(3-oxopropyl)-1H-1,2,4-triazol-3-yl]thiophene-2-carbonitrile**

10 To a solution of 3,4-dimethyl-5-(1H-1,2,4-triazol-3-yl)thiophene-2-carbonitrile (0.037g) in anhydrous acetonitrile (1mL) acrylaldehyde (0.040mL) was added and the resulting solution was heated to 50°C for 5h. Solvent evaporation under vacuum gave the title compound (0.046g).

$m/z$  ( $[MH]^+$ )=261

#### **Intermediate 114**

##### **3-Quinolin-3-yl-propionaldehyde**

15 To a solution of oxalyl chloride (0.290mL) in anhydrous DCM (8mL) cooled to -78°C under nitrogen atmosphere DMSO (0.340mL) was slowly added. After 1h at -78°C a solution of 3-quinolin-3-ylpropan-1-ol (0.300g) in anhydrous DCM (3mL) was added. After stirring at -  
20 40°C for 3h TEA(0.892mL) was added and the reaction mixture was allowed to reach room temperature. Water (10mL) was added and the mixture was extracted with DCM (3x10mL), the organic phase dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give the title compound (0.290g)

$m/z$  ( $[MH]^+$ )=186.

25

#### **Intermediate 115**

##### **3-[4-(3-Nitrophenyl)-1H-imidazol-1-yl]propanal**

To a solution of 4-(3-nitrophenyl)-1H-imidazole (0.040g) in anhydrous acetonitrile (5mL) acrylaldehyde (0.120mL) was added and the resulting solution was heated to 80°C and stirred  
30 for 4 days. The solvent was removed under reduced pressure to give the title compound (0.041g).

$m/z$  ( $[MH]^+$ ) = 246.

#### **Intermediate 116**

##### **1-(2,3-Dihydro-1,4-benzodioxin-6-yl)butane-1,4-diol**

35 To a solution of lithium aluminum hydride (1M in THF, 9.53mL) in anhydrous THF (15mL) cooled to 0°C a solution of 4-(2,3-dihydro-1,4-benzodioxin-6-yl)-4-oxobutyric acid (0.750g) in anhydrous THF (5mL) was added dropwise. The reaction mixture was heated to reflux for 24h, then it was cooled to room temperature and diluted with EtOAc (10mL). After  
40 evaporation of the solvents under reduced pressure the crude material was treated with a 1N HCl aqueous solution (20mL) and DCM (100mL). The organic phase was washed with a saturated NaHCO<sub>3</sub> aqueous solution (50mL), brine (50mL), dried over Na<sub>2</sub>SO<sub>4</sub> and



concentrated under reduced pressure. The crude material was purified by flash chromatography (EtOAc/cyclohexane from 50\50 to 100\0) to give the title compound (0.340g).

m/z ([MH]<sup>+</sup>)=225

5

#### **Intermediate 117**

##### **4-(2,3-Dihydro-1,4-benzodioxin-6-yl)-4-oxobutanal**

To a solution of oxalyl chloride (0.560mL) in anhydrous DCM (5mL) cooled to -78°C under nitrogen atmosphere a solution of DMSO (0.910mL) in anhydrous DCM (5mL) was slowly added. After stirring for 30min at -78°C a solution of intermediate **116** (0.340g) in anhydrous DCM (2mL) was added dropwise. The reaction mixture was stirred at -40°C for 3h then TEA(2.5mL) was added and then the reaction mixture was allowed to reach room temperature. A saturated NaHCO<sub>3</sub> aqueous solution (20mL) was added and the mixture extracted with DCM (3x20mL). The organic phase was washed with brine (20mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (EtOAc/cyclohexane 40\60) to give the title compound (0.250g).

15

m/z ([MH]<sup>+</sup>)=221

#### **Intermediate 118**

##### **1-[2-(1,3-Dioxolan-2-yl)ethyl]-5-methoxy-1H-pyrrolo[3,2-b]pyridine**

To a solution of 5-methoxy-1H-pyrrolo[3,2-b]pyridine (0.040g) in anhydrous THF (1.5mL) cooled to 0°C, sodium hydride (0.010g) was added under nitrogen atmosphere. The mixture was stirred at room temperature for 1h then 2-(2-bromoethyl)-1,3-dioxolane (0.038mL) was added and the stirring continued for an additional 6h. The reaction mixture was quenched with water (3mL) and extracted with DCM (3x5mL), the organic phase dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give the title compound (0.067).

25

m/z ([MH]<sup>+</sup>)=249.

#### **Intermediate 119**

##### **2-[1-(2,2-Dimethoxyethyl)-1H-pyrazol-3-yl]-1,3-thiazole**

To a stirred suspension of sodium hydride (0.005g) in anhydrous DMF (0.5mL) at 0°C, under nitrogen atmosphere, a solution of 2-(1H-pyrazol-3-yl)-1,3-thiazole (0.030g) in anhydrous DMF (1mL) was added. The mixture was allowed to reach room temperature and stirred for an additional 15min and then a solution of bromoacetaldehyde dimethylacetal (0.024mL) in anhydrous DMF (0.5mL) was added. After stirring the reaction mixture at room temperature for 24h, the solvent was evaporated under reduced pressure and the crude material purified by flash chromatography (eluting with: DCM) to give the title compound (0.015g).

35

m/z ([MH]<sup>+</sup>) = 240.

#### **Intermediate 120**

##### **1-(2,2-Dimethoxyethyl)-4-phenyl-1H-imidazole**

40

To a stirred suspension of sodium hydride (0.005g) in anhydrous DMF (0.7mL) at 0°C a solution of 4-phenyl-1*H*-imidazole (0.023g) in anhydrous DMF (1mL) was added under nitrogen atmosphere. The mixture was allowed to reach room temperature and stirred for an additional 15min, then a solution of bromoacetaldehyde dimethylacetal (0.022mL) in anhydrous DMF (0.7mL) was added. After stirring the reaction mixture at room temperature for 24h the solvent was evaporated under reduced pressure and the crude material purified by flash chromatography (eluting with: DCM/MeOH from 100\0 to 90\10) to give the title compound (0.027g).

$m/z$  ( $[MH]^+$ ) = 233.

#### Intermediate 121

##### 1-(2,2-Dimethoxyethyl)-4-thien-2-yl-1*H*-imidazole

To a stirred suspension of sodium hydride (0.019g) in anhydrous DMF (3mL) at 0°C, under nitrogen atmosphere, a solution of 4-thien-2-yl-1*H*-imidazole (0.100g) in anhydrous DMF (1mL) was added. The mixture was allowed to reach room temperature, stirred for an additional 15min and then a solution of bromoacetaldehyde dimethylacetal (0.090mL) in anhydrous DMF (1mL) was added. After stirring at room temperature for 24h the solvent was evaporated under reduced pressure and the crude material purified by flash chromatography (eluting with: DCM/MeOH from 100\0 to 99\1) to give the title compound (0.088g).

$m/z$  ( $[MH]^+$ ) = 239.

#### Example 1

##### (11*S*,21*R*)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(cyano)-methylene]-erythromycin A

To a solution of intermediate **3** (0.060g) in anhydrous DMF (16mL) potassium cyanide (0.051g) was added under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 2h, quenched with a saturated NaHCO<sub>3</sub> aqueous solution (30mL) and extracted with DCM (3x30mL). The organic phase was then washed with brine (30mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH 95\5) to give the title compound (0.017g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 5.27(dd, 1H), 4.74 (dd, 1H), 4.62 (d, 1H), 4.42 (d, 1H), 4.26 (d, 1H), 3.84 (q, 1H), 3.56 (m, 1H), 3.16 (m, 1H), 3.10-3.0 (m, 2H), 2.77(s, 3H), 2.68 (m, 1H), 2.60 (m, 1H), 2.25 (s, 6H), 2.05 (m, 3H), 1.90 (m, 1H), 1.68 (m, 1H), 1.63 (m, 2H), 1.56 (s, 3H), 1.39 (d, 3H), 1.35 (m, 1H), 1.30 (s, 3H), 1.26 (d, 3H), 1.18 (d, 3H), 1.14 (d, 3H), 1.06 (d, 3H), 0.92 (t, 3H).

TLC: DCM/MeOH 95\5 (R<sub>f</sub>=0.57).

#### Example 2

##### (11*S*,21*R*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(cyano)-methylene]-erythromycin A

A solution of example 1 (0.024g) in MeOH (1mL) was stirred for 24h then concentrated under reduced pressure to give the title compound (0.020g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 5.26 (dd, 1H), 4.61 (d, 1H), 4.34 (d, 1H), 4.28 (m, 1H), 3.87 (q, 1H), 3.57 (m, 1H), 3.18 (m, 1H), 3.15 (t, 1H), 3.12 (m, 1H), 3.06 (m, 1H), 2.78 (s, 3H), 2.62 (m, 1H), 2.46 (m, 1H), 2.27 (s, 6H), 1.91 (m, 1H), 1.84 (m, 1H), 1.70 (m, 1H), 1.68 (m, 1H), 1.62 (m, 1H), 1.57 (s, 3H), 1.41 (d, 3H), 1.34 (d, 3H), 1.34 (s, 3H), 1.24 (m, 1H), 1.26 (d, 3H), 1.14 (d, 3H), 1.07 (d, 3H), 0.92 (t, 3H).  
TLC: DCM/MeOH 90/10 (R<sub>f</sub>=0.38).

### Example 3

#### (11*S*,21*R*)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-oxycarbonyl-(aminomethyl)-methylene]-erythromycin A

To a solution of intermediate **4** (0.036g) in iPrOH (1.5mL), sodium cyanoborohydride (0.023g) and titanium(III) chloride (10 wt.% solution in 20/30 wt.% hydrochloric acid, 0.1mL) were added portionwise within 6h. The mixture was diluted with a saturated NaHCO<sub>3</sub> aqueous solution (3x2mL), extracted with DCM (3x2mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH/NH<sub>4</sub>OH 100/0/0, 98/2/0, 95/5/0.5) to give the title compound (0.010g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 5.06 (dd, 1H), 4.76 (dd, 1H), 4.38 (d, 1H), 4.17 (d, 1H), 3.80 (q, 1H), 3.54 (bm, 1H), 3.24 (m, 1H), 3.20-3.00 (m, 4H), 2.64 (s, 3H), 2.60 (m, 1H), 2.54 (m, 1H), 2.25 (s, 1H+6H), 2.08 (s, 3H), 1.94 (m, 1H), 1.74 (m, 1H), 1.70-1.50 (m, 3H), 1.40 (d, 3H), 1.30 (m, 1H), 1.30(s, 3H), 1.26 (d, 3H), 1.17 (d, 3H), 1.16 (d, 3H), 1.12 (d, 3H), 0.86 (t, 3H).

### Example 4

#### (11*S*,21*R*,*S*)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-oxycarbonyl-(benzhydrylideneamino)-methylene]-erythromycin A

To a solution of intermediate **18** (1.5g) and EDC (3.1g) in DCM (100mL) cooled to 0°C, DMSO (3.45mL) was added under nitrogen atmosphere. After stirring at 0°C for 10min, a solution of pyridinium trifluoroacetate (3.12g) in anhydrous DCM (15mL) was slowly added. After 10min the ice-bath was removed. The reaction mixture was stirred for 3h at room temperature then quenched with water (150mL) and extracted with DCM (3x250mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH 95/5) to give the title compound (1.2g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.80-7.20 (m, 10H), 6.40 (dd, 1H), 5.15 (s, 1H), 4.73 (m, 1H), 4.42 (d, 1H), 4.16 (d, 1H), 3.90 (q, 1H), 3.55 (m, 1H), 3.17 (m, 1H), 2.95 (m, 1H), 2.94 (d, 1H), 2.67 (m, 1H), 2.53 (s, 3H), 2.43 (m, 1H), 2.33 (s, 6H), 2.05 (s, 3H), 2.00 (m, 1H), 1.74 (m, 1H), 1.65 (m, 1H), 1.53 (s, 3H), 1.38 (d, 3H), 1.23 (s, 3H), 1.29 (d, 3H), 1.25 (m, 1H), 1.25 (d, 3H), 1.14 (d, 3H), 1.07 (d, 3H), 0.83 (t, 3H).

TLC: DCM/MeOH 10/1 (R<sub>f</sub>=0.30).

### Example 5

**(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(benzhydrylideneamino)-methylene]-erythromycin A**

A solution of example 4 (0.030g) in MeOH (1mL) was stirred at room temperature overnight. Solvent evaporation under reduced pressure gave the title compound (0.024g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.80-7.20 (m, 10H), 6.38 (dd, 1H), 5.13 (s, 1H), 4.34 (d, 1H), 4.18 (d, 1H), 3.91 (q, 1H), 3.55 (m, 1H), 3.20 (m, 1H), 2.96 (m, 1H), 2.63 (s, 1H), 2.53 (s, 1H), 2.44 (m, 2H), 2.26 (s, 6H), 2.00 (m, 1H), 1.70-1.45 (m, 7H), 1.45 (d, 1H), 1.30 (m, 4H), 1.04 (d, 3H), 0.96 (t, 3H), 0.91 (d, 3H).

TLC: DCM/MeOH 10\1 (R<sub>f</sub>=0.34).

10

**Example 6**

**(11S,21R,S)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A**

A solution of example 4 (1.1g) in acetonitrile (30mL) and a 1.2N HCl aqueous solution (70mL) was stirred at room temperature for 1h. After neutralising the mixture with solid Na<sub>2</sub>CO<sub>3</sub> and evaporating the solvent, the aqueous phase was extracted with DCM (3x200mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give the title compound (0.9g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 5.45 (dd, 1H), 4.75 (m, 1H), 4.45 (d, 1H), 4.40 (d, 1H), 4.21 (d, 1H), 3.82 (q, 1H), 3.54 (m, 1H), 3.09 (m, 1H), 2.69 (m, 1H), 2.68 (s, 3H), 2.58 (m, 1H), 2.41 (m, 1H), 2.25 (s, 6H), 2.07 (m, 3H), 1.95 (m, 1H), 1.75 (m, 1H), 1.60 (m, 1H), 1.49 (s, 3H), 1.39 (d, 3H), 1.35 (m, 1H), 1.31 (s, 3H), 1.26 (d, 3H), 1.17 (d+d, 6H), 1.09 (d, 3H), 0.88 (t, 3H).

TLC: DCM/MeOH 10\1 (R<sub>f</sub>=0.48).

**Example 7**

**(11S,21S)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A**

To a solution of example 6 (15.1g) in anhydrous toluene (170mL) fresh distilled benzaldehyde (2.52mL) and pyridine (2.01mL) were added and the reaction mixture was refluxed for 4.5h. After evaporating the solvent the residue was dissolved in acetonitrile (60mL) then a 1.2N HCl aqueous solution (120mL) was added at room temperature. After stirring for 1.5h the solvent was evaporated and the aqueous acid solution extracted with EtOAc (150mL) and DCM (150mL). The aqueous phase was neutralized with solid potassium carbonate and extracted with EtOAc (2x150mL). The collected organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give the title compound (11.5g, 96% pure by NMR analysis).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 5.45 (dd, 1H), 4.75 (m, 1H), 4.45 (d, 1H), 4.40 (d, 1H), 4.21 (d, 1H), 3.82 (q, 1H), 3.54 (m, 1H), 3.09 (m, 1H), 2.69 (m, 1H), 2.68 (s, 3H), 2.58 (m, 1H), 2.41 (m, 1H), 2.25 (s, 6H), 2.07 (m, 3H), 1.95 (m, 1H), 1.75 (m, 1H), 1.60 (m, 1H), 1.49 (s, 3H), 1.39 (d, 3H), 1.35 (m, 1H), 1.31 (s, 3H), 1.26 (d, 3H), 1.17 (d+d, 6H), 1.09 (d, 3H), 0.88 (t, 3H).

40

**Example 8**

**(11S,21S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A**

A solution of example 7 (0.012g) in MeOH (1mL) was stirred at room temperature overnight. After evaporating the solvent under reduced pressure the crude material was purified by flash chromatography (eluting with: DCM\MeOH 100\5) to give the title compound (0.007g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 5.41 (dd, 1H), 4.42 (d, 1H), 4.33 (d, 1H), 4.22 (d, 1H), 3.83 (q, 1H), 3.56 (m, 1H), 3.23 (d, 1H), 3.12 (m, 1H), 3.02 (m, 1H), 2.80 (d, 1H), 2.69 (s, 3H), 2.60 (m, 1H), 2.54 (m, 1H), 2.40 (d, 1H), 2.33 (s, 6H), 1.95 (m, 1H), 1.9-1.50 (m, 3H), 1.49 (s, 3H), 1.39 (d, 3H), 1.35 (m, 1H), 1.33 (s, 3H), 1.32 (m, 1H), 1.31 (d, 3H), 1.26 (d, 3H), 1.16(d, 3H), 1.10 (d, 3H), 0.88 (t, 3H).

**Example 9**

**(10R,S,11R)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonylmethylene]-erythromycin A**

To a solution of intermediate **23** (0.050g) in anhydrous DCM (25mL), EDC (0.102g) and DMSO (0.115mL) were added under nitrogen atmosphere. The mixture was cooled to 0°C and a solution of pyridinium trifluoroacetate (0.102g) in DCM (0.5mL) was added dropwise. The mixture was allowed to reach room temperature; after stirring for 5h water (10mL) was added and the mixture extracted with DCM (2x20mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure and the crude material purified by preparative TLC (eluting with: DCM\MeOH 95\5). The recovered silica gel was stirred for 18h in MeOH (2mL), the mixture was filtered and solvent evaporation under reduced pressure gave the title compound (0.025g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 4.90 (dd, 1H), 4.32 (d, 1H), 4.24 (d, 1H), 3.85 (q, 1H), 3.56 (m, 1H), 3.32 (d, 1H), 3.18 (m, 1H), 3.12 (m, 1H), 3.02 (m, 1H), 2.80 (d, 1H), 2.71 (dd, 1H), 2.63 (s, 3H), 2.55 (m, 1H), 2.47 (m, 1H), 2.27 (s, 6H), 1.87 (m, 1H), 1.70 (m, 1H), 1.62 (m, 1H), 1.58 (m, 1H), 1.50 (s, 3H), 1.38 (d, 3H), 1.30 (d, 3H), 1.31 (s, 3H), 1.30 (m, 1H), 1.25 (d, 3H), 1.22 (m, 1H), 1.14 (d, 3H), 1.07 (d, 3H), 0.86 (t, 3H).

**Example 10**

**(11S,21S)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-2-fluoro-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A**

To a solution of example 7 (0.284g) in anhydrous THF (14mL) cooled to -10°C potassium *tert*-butoxide (1M in THF, 0.553mL) was added under nitrogen atmosphere. After 5min *N*-fluorobenzenesulfonimide (0.148g) was added at -10°C. The mixture was stirred at room temperature for 1h. The reaction mixture was diluted with DCM (15mL) and washed with water (15mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The crude material was purified by flash chromatography (eluting with: DCM\MeOH\NH<sub>4</sub>OH from 100\0\0, to 94\6\0.2) to give the title compound (0.120g).

m/z ([MH]<sup>+</sup>) = 687.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 5.35 (dd, 1H), 4.74 (M, 1H), 4.48 (d, 1H), 4.33 (d, 1H), 3.96 (m, 1H), 3.52 (m, 1H), 2.89 (s, 3H), 2.86 (m, 1H), 2.72 (m, 1H), 2.53 (m, 1H), 2.27 (s, 6H), 2.08 (s,

3H), 2.0-1.94 (m, 2H), 1.82 (d, 3H), 1.76 (m, 1H), 1.64 (m, 1H), 1.48 (d+m, 3H+1H), 1.31 (s, 3H), 1.26 (m, 6H), 1.16 (d, 3H), 1.08 (d, 3H), 0.92 (t, 3H).

#### **Example 11**

5 **(11S,21S)-3-Decladinosyl-11,12-dideoxy-2-fluoro-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A**

A solution of example 10 (0.010g) in MeOH (1mL) was stirred at room temperature overnight. Evaporation of the solvent under reduced pressure gave the title compound (0.005g).

10 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 5.33 (dd, 1H), 4.42 (d, 1H), 4.33 (d, 1H), 4.03 (dd, 1H), 3.53 (bm, 1H), 3.18 (m, 1H), 3.10 (m, 1H), 2.93 (s, 3H), 2.90 (m, 1H), 2.54 (m, 2H), 2.30 (s, 6H), 2.09 (s, 1H), 2.06 (m, 1H), 1.96 (m, 1H), 1.82 (d, 1H), 1.62-1.50 (m, 6H), 1.34 (s, 3H), 1.27(m, 4H), 1.26 (s, 3H), 1.16 (d, 3H), 1.08 (d, 3H), 0.92 (t, 3H).

15 **Example 12**

**(11S,21S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(N-*t*-butylcarbamate)-ethylamino)-methylene]-erythromycin A**

To a solution of example 7 (1.34g) in anhydrous acetonitrile (12mL) *tert*-butyl *N*-(2-oxoethyl)carbamate (0.640g) was added under nitrogen atmosphere and the resulting mixture was stirred for 24h at room temperature. Sodium cyanoborohydride (1M in THF, 2.0mL) and acetic acid (0.114mL) were added and the reaction mixture was stirred for 12h at room temperature. After evaporating the solvent, the residue was dissolved in DCM (100mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (50mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was diluted in MeOH (35mL) and refluxed for 15 h. The solvent was evaporated under reduced pressure and the crude material purified by flash chromatography (eluting with: cyclohexane\acetone 85\15) to give the title compound (1.51g, % pure by NMR analysis).

*m/z* ([MH]<sup>+</sup>) = 770.

30 **Example 13**

**(11S,21S)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A**

To a solution of example 11 (1.5g) in anhydrous DCM (5.4mL) trifluoroacetic acid (0.6mL) was added under nitrogen atmosphere and the resulting mixture was stirred for 2h at room temperature. The reaction mixture was diluted with EtOAc (15mL) and concentrated under reduced pressure. The residue was dissolved in DCM (100mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (50mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give the title compound (1.05g).

*m/z* ([MH]<sup>+</sup>) = 670.

40 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 5.12 (dd, 1H), 4.32 (d, 1H), 4.21 (d, 1H), 4.05 (m, 1H), 3.85 (q, 1H), 3.58 (m, 1H), 3.25 (dd, 1H), 3.20-3.0 (m, 4H), 3.05 (m, 2H), 2.67 (m, 1H), 2.68 (s, 3H), 2.61 (m, 1H), 2.40 (s, 6H), 2.32 (m, 1H), 1.91 (m, 1H), 1.78-1.68 (m, 3H), 1.60 (m, 1H), 1.47 (s,

3H), 1.38 (d, 3H), 1.32 (s, 3H), 1.30 (d, 3H), 1.29 (m, 1H), 1.27 (d, 3H), 1.15 (d, 3H), 1.11 (d, 3H), 0.88 (t, 3H).

#### **Example 14**

5 **(11S,21R)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-oxycarbonyl-(3-quinolinyl-carbonylaminomethyl)-methylene]-erythromycin A**

To a solution of intermediate **25** (0.035g) in anhydrous DCM (1.5mL), EDC (0.041g) and DMSO (0.041mL) were added at 0°C under nitrogen atmosphere. After stirring at 0°C for 15min, pyridinium trifluoroacetate (0.042g) was added. The reaction mixture was stirred for 10 3h at room temperature, then quenched with water (3mL) and extracted with DCM (5mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by preparative TLC (eluting with: DCM/MeOH 95/5) to give the title compound (0.016g).

m/z ([MH]<sup>+</sup>) = 838.

15

#### **Example 15**

**(11S,21R)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-quinolinyl-carbonylaminomethyl)-methylene]-erythromycin A**

A solution of example **14** (0.016g) in MeOH (1.5mL) was stirred for 24h then concentrated under reduced pressure to give the title compound (0.009g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 9.50 (d, 1H), 8.79 (d, 1H), 8.16 (d, 1H), 7.94 (d, 1H), 7.84 (t, NH), 7.81 (t, 1H), 7.61 (t, 1H), 4.90 (dd, 1H), 4.27 (d, 1H), 4.19 (d, 1H), 4.01 (m, 2H), 3.84 (d, 1H), 3.52 (m, 3H), 3.14 (m, 3H), 2.70 (m, 1H), 2.53 (s, 3H), 2.54 (m, 1H), 2.43 (m, 1H), 2.27 (s, 6H), 1.95 (m, 1H), 1.84 (d, 1H), 1.75 (m, 1H), 1.64 (m, 1H), 1.60 (m, 1H), 1.56 (s, 3H), 1.38 (d, 3H), 1.30 (d, 3H), 1.26 (s, 3H), 1.22 (m, 1H), 1.22 (d, 3x3H), 0.88 (t, 3H).

25

#### **Example 16**

**(11S,21R)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-oxycarbonyl-(4-(4-(pyridin-3-yl)-imidazol-1-yl)-butyramidomethyl)-methylene]-erythromycin A**

30

To a solution of intermediate **26** (0.040g) in anhydrous DCM (3mL) Dess-Martin periodinane (0.030g) was added portionwise at room temperature within 5h. The reaction was quenched with a Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution (5% in a saturated NaHCO<sub>3</sub> aqueous solution, 2mL), stirred for 1h then extracted with DCM (10mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH 95/5) to give the title compound (0.029g).

35

TLC: DCM/MeOH 90/10 (R<sub>f</sub>=0.42).

#### **Example 17**

40 **(11S,21R)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(4-(pyridin-3-yl)-imidazol-1-yl)-butyramidomethyl)-methylene]-erythromycin A**

A solution of example 16 (0.029g) in MeOH (2mL) was stirred for 24h then concentrated under reduced pressure to give the title compound (0.023g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.98 (d, 1H), 8.40 (dd, 1H), 8.10 (dd, 1H), 7.61 (d, 1H), 7.35 (d, 1H), 7.29 (m, 1H), 6.48 (t, NH), 4.89 (dd, 1H), 4.30 (d, 2H), 4.21 (d, 1H), 4.01 (m, 1H), 3.83 (q, 1H), 3.73 (m, 1H), 3.55 (m, 1H), 3.34 (m, 1H), 3.19 (m, 1H), 3.08 (m, 2H), 2.65 (s, 3H), 2.58 (m, 1H), 2.47 (m, 1H), 2.34 (m, 1H), 2.28 (s, 6H), 2.3-2.1 (m, 4H), 1.91 (m, 1H), 1.81 (m, 1H), 1.80-1.54 (m, 3H), 1.51 (s, 3H), 1.39 (d, 3H), 1.35 (m, 1H), 1.32 (s, 3H), 1.30 (d, 3H), 1.25 (d, 3H), 1.12 (d, 3H), 1.15(d, 3H), 1.12 (d, 3H), 0.87 (t, 3H).

**Example 18**

(11S,21R)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(4-(pyridin-3-yl)-imidazol-1-yl)-propionamidomethyl)-methylene]-erythromycin A

To a solution of intermediate 27 (0.039g) in anhydrous DCM (3mL) under nitrogen atmosphere Dess Martin periodinane (0.030g) was added portionwise at room temperature within 5h. The reaction was quenched with a Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution (5% in a saturated NaHCO<sub>3</sub> aqueous solution, 7mL), stirred for 1h and then extracted with DCM (15mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH 95/5) to give the title compound (0.026g).

TLC: DCM/MeOH 90/10 (R<sub>f</sub>=0.35).

**Example 19**

(11S,21R)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(4-(pyridin-3-yl)-imidazol-1-yl)-propionamidomethyl)-methylene]-erythromycin A

A solution of example 18 (0.024g) in MeOH (1mL) was stirred for 24h then concentrated under reduced pressure to give the title compound (0.020g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.99 (d, 1H), 8.45 (dd, 1H), 8.08 (dd, 1H), 7.58 (d, 1H), 7.35 (d, 1H), 7.29 (m, 1H), 6.67 (t, NH), 4.80 (dd, 1H), 4.36 (m, 2H), 4.30 (d, 1H), 4.19 (d, 1H), 3.83 (m, 2H), 3.61 (m, 1H), 3.55 (m, 1H), 3.25 (m, 2H), 3.04 (m, 2H), 2.70 (m, 2H), 2.62 (s, 3H), 2.58 (m, 2H), 2.33 (s, 6H), 2.32 (d, 1H), 1.85 (m, 1H), 1.80 (m, 1H), 1.70 (m, 2H), 1.56 (m, 1H), 1.48 (s, 3H), 1.45 (d, 3H), 1.33 (s, 3H), 1.21 (d, 3H), 1.35 (m, 1H), 1.18 (d, 3H), 1.04 (d, 3H), 0.95 (t, 3H), 0.91 (d, 3H).

**Example 20**

(11S,21R)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(4-(pyridin-3-yl)-imidazol-1-yl)-acetamidomethyl)-methylene]-erythromycin A

To a solution of intermediate 28 (0.018g) in anhydrous DCM (1.5mL) under nitrogen atmosphere Dess-Martin periodinane (0.020g) was added portionwise at room temperature within 5h. The reaction was quenched with a Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution (5% in a saturated NaHCO<sub>3</sub> aqueous solution, 2mL), stirred for 1h then extracted with DCM (10mL). The organic phase



was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by preparative TLC (eluting with: DCM/MeOH 10\1) and the recovered silica gel was stirred overnight in MeOH (1mL). The mixture was filtered and solvent evaporation under reduced pressure gave the title compound (0.009g).

5 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 9.02 (d, 1H), 8.49 (m, 1H), 8.11 (m, 1H), 7.65 (d, 1H), 7.43 (d, 1H), 7.30 (m, 1H), 6.58 (t, NH), 4.89 (dd, 1H), 4.70 (dd, 2H), 4.29 (d, 1H), 4.20 (d, 1H), 3.83 (m, 2H), 3.69 (m, 1H), 3.51 (m, 1H), 3.29 (m, 1H), 3.17 (m, 1H), 3.04 (m, 2H), 2.60 (s, 3H), 2.54 (m, 1H), 2.44 (m, 1H), 2.31 (m, 1H), 2.27 (s, 6H), 1.91 (m, 1H), 1.80 (m, 1H), 1.68 (m, 2H), 1.60 (m, 1H), 1.49 (s, 3H), 1.39 (d, 3H), 1.29 (s, 3H), 1.29 (d, 3H), 1.22 (m, 1H), 1.25 (d, 3H), 1.12 (d, 3H), 1.10 (d, 3H), 0.87 (t, 3H).

#### Example 21

##### (11*S*,21*R*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(1-(pyrrolidin-2-one)-methyl)-methylene]-erythromycin A

15 To a solution of intermediate **29** (0.020g) in anhydrous DCM (2mL) under nitrogen atmosphere Dess-Martin periodinane (0.017g) was added portionwise at room temperature within 1h. After stirring for 5h the reaction was quenched with a solution Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (5% in a saturated NaHCO<sub>3</sub> aqueous solution, 2mL), stirred for 1h then extracted with DCM (3x5mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH from 100\0 to 95\5) to give a compound that was dissolved in MeOH (2mL) and stirred at room temperature overnight. Evaporation of the solvent gave the title compound (0.010g).

20 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 4.39 (m, 1H), 3.76 (m, 1H), 3.52 (m, 1H), 3.39 (m, 1H), 3.15 (m, 1H), 3.04 (m, 1H), 2.41 (m, 1H), 2.36 (m, 1H), 2.32 (m, 1H), 2.10 (m, 1H), 2.02 (m, 1H), 1.12 (d, 3H).

#### Example 22

##### (11*S*,21*R*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(quinoxalin-2-ylsulfanyl)-acetamidomethyl)-methylene]-erythromycin A

30 To a solution of intermediate **30** (0.068g) in anhydrous DCM (5mL) Dess-Martin periodinane (0.064g) was added under nitrogen atmosphere. The mixture was stirred at room temperature for 6h. The reaction was quenched with a solution Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (5% in a saturated NaHCO<sub>3</sub> aqueous solution, 5mL), stirred for 30min and then extracted with DCM (3x4mL). The organic phase was washed with brine (5mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was dissolved in MeOH (5mL) and stirred overnight. Solvent evaporation under reduced pressure gave the title compound (0.053g).

35 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.70 (s, 1H), 8.05 (d, 1H), 8.02 (d, 1H), 7.71 (td, 1H), 7.64 (td, 1H), 7.59 (bt, 1H), 4.11 (d, 1H), 4.03 (m, 1H), 3.34 (bm, 1H), 2.98 (m, 1H), 1.01 (d, 3H).

#### Example 23

**(11S,21R)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-quinoxalin-2-ylsulfanyl)-propionamidomethyl]-methylene]-erythromycin A**

To a solution of intermediate **31** (0.035g) in anhydrous DCM (2.5mL) Dess-Martin periodinane (0.033g) was added under nitrogen atmosphere. The mixture was stirred at room temperature for 18h. The reaction was quenched with a Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution (5% in a saturated NaHCO<sub>3</sub> aqueous solution, 2mL), stirred for 30min and then extracted with DCM (3x4mL). The organic phase was washed with brine (3mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was dissolved in anhydrous MeOH (2mL) and stirred overnight. The solvent was evaporated under reduced pressure and the crude material purified by flash chromatography (eluting with: DCM/MeOH from 100/0 to 95/5) to give the title compound (0.011g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.50 (s, 1H), 8.00 (d, 1H), 7.98 (d, 1H), 7.70 (t, 1H), 7.61 (t, 1H), 6.69 (bt, 1H), 3.83 (m, 1H), 3.68 (m, 1H), 3.64 (m, 1H), 3.34 (m, 1H), 3.06 (m, 1H), 2.77 (m, 1H), 2.34 (m, 1H), 1.11 (d, 3H).

**Example 24**

**(11S,21R)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-[(quinolin-4-ylmethylene)-amino]-methyl]-methylene]-erythromycin A**

To a solution of intermediate **32** (0.100g) in anhydrous DCM (4mL) Dess Martin periodinane (0.110g) was added portionwise within 3h under nitrogen atmosphere. The mixture was stirred at room temperature for 3h. The reaction was quenched with a Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution (5% in a saturated NaHCO<sub>3</sub> aqueous solution, 2mL), stirred for 45min and then extracted with DCM (3x4mL). The organic phase was washed with brine (3mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by preparative TLC (eluting with: DCM/MeOH 95/5), the recovered silica gel stirred for 18h in MeOH (5mL), the mixture filtered and then solvent evaporation under reduced pressure gave the title compound (0.015g).

m/z ([MH]<sup>+</sup>) = 780.

**Example 25**

**(11S,21R)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-[(quinolin-4-ylmethyl)-amino]-methyl]-methylene]-erythromycin A**

To a solution of example **24** (0.015g) in anhydrous MeOH (6mL) palladium (10wt. % on carbon powder, 0.005g) was added and the mixture stirred under hydrogen atmosphere (6 atm) for 20h. Filtration through a celite pad eluting with MeOH (20mL) and purification by flash chromatography (eluting with DCM/MeOH from 100/0 to 95/5) and by preparative TLC (eluting with: DCM/MeOH/NH<sub>4</sub>OH 87.5/12.5/0.5) gave the title compound (0.002g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.87 (d, 1H), 8.10 (d, 2H), 7.61 (d, 1H), 7.70 (m, 1H), 7.57 (m, 1H), 4.38 (d, 1H), 4.26 (d, 1H), 3.55 (m, 1H), 3.28÷3.00 (m, 2H).

**Example 26**

**(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(4-(pyridin-3-yl)-imidazol-1-yl)-propionamido)-methylene]-erythromycin A**

To a solution of example 6 (0.020g) in anhydrous DMF (2mL) under nitrogen atmosphere intermediate 48 (0.009g), HATU (0.013g) and DIPEA (0.013mL) were sequentially added.

- 5 The reaction mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, the residue dissolved in DCM (15mL) and washed with water (10mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM\MeOH 95\5) to give a compound that was dissolved in MeOH (1mL) and stirred at room temperature overnight. Solvent evaporation under reduced pressure gave the title compound (0.009g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 9.04 (d, 1H), 8.44 (dd, 1H), 8.13 (m, 1H), 7.61 (m, 1H), 7.41 (d, 1H), 6.73 (bd, 1H), 5.08 (dd, 1H), 4.94 (m, 1H), 4.45 (m, 1H), 4.26 (m, 1H), 4.25 (d, 1H), 4.08 (m, 3H), 3.80 (q, 1H), 3.51 (m, 1H), 3.15 (m, 1H), 3.04 (m, 1H), 2.98 (m, 1H), 2.65 (m, 1H), 2.60 (m, 1H), 2.52 (m, 1H), 2.44 (m, 1H), 2.39 (s, 3H), 2.34 (m, 1H), 2.26 (s, 6H), 1.90 (m, 1H), 15 1.75 (m, 1H), 1.65-1.55 (m, 3H), 1.48 (s, 3H), 1.37 (d, 3H), 1.27 (d, 3H), 1.22 (d, 3H), 1.25 (m, 1H), 1.17 (s, 3H), 1.16 (d, 3H), 1.12 (d, 3H), 0.87 (t, 3H).

**Example 27**

- 20 **(11*S*,21*R*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(4-(pyridin-3-yl)-imidazol-1-yl)-butyramido)-methylene]-erythromycin A**  
and

**Example 28**

- (11*S*,21*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(4-(pyridin-3-yl)-imidazol-1-yl)-butyramido)-methylene]-erythromycin A**

- 25 To a solution of example 6 (0.020g) in anhydrous DMF (2mL) under nitrogen atmosphere intermediate 49 (0.009g), HATU (0.013g) and DIPEA (0.013mL) were sequentially added. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, the residue dissolved in DCM (15mL) and washed with water (10mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure.
- 30 The crude material was purified by flash chromatography (eluting with: DCM\MeOH 95\5, 90\10) and the (21*R*) and (21*S*) isomers were isolated. Each isomer was dissolved in MeOH (1mL) and stirred at room temperature overnight. Evaporation of the solvent under reduced pressure gave the title compound 27 (0.003g) and the title compound 28 (0.006g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (example 27): 8.98 (d, 1H), 8.89 (bd, 1H), 8.46 (d, 1H), 8.08 (d, 1H), 7.61 (d, 1H), 7.41 (d, 1H), 7.28 (m, 1H), 5.33 (dd, 1H), 5.22 (dd, 1H), 4.31 (d, 1H), 4.25 (d, 1H), 35 4.14 (m, 2H), 3.88 (q, 1H), 3.56 (m, 1H), 3.27 (m, 1H), 3.17 (dd, 1H), 3.06 (m, 1H), 2.99 (m, 1H), 2.66 (m, 1H), 2.57 (s, 3H), 2.46 (m, 1H), 2.40 (m, 2H), 2.27 (s, 6H), 2.21 (m, 2H), 1.86 (m, 1H), 1.84 (m, 1H), 1.70-1.50 (m, 3H), 1.54 (s, 3H), 1.36 (d, 3H), 1.33 (d, 3H), 1.29 (s, 3H), 1.25 (m, 1H), 1.24 (d, 3H), 1.17 (d, 3H), 1.08 (d, 3H), 0.90 (t, 3H).

40 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (example 28): 9.02 (d, 1H), 8.46 (dd, 1H), 8.11 (m, 1H), 7.61 (m, 1H), 7.37 (d, 1H), 7.31 (m, 1H), 6.47 (bd, 1H), 5.26 (dd, 1H), 4.81 (bt, 1H), 4.29 (d, 1H), 4.13 (m, 3H), 3.81 (q, 1H), 3.54 (m, 1H), 3.17 (m, 1H), 3.08-3.04 (m, 2H), 2.53 (s, 3H), 2.56 (m, 1H),

2.45 (m, 1H), 2.36 (m, 1H), 2.27 (s, 6H), 2.17-2.13 (m, 4H), 2.00 (m, 1H), 1.80 (m, 1H), 1.68 (m, 1H), 1.60 (m, 1H), 1.51 (s, 3H), 1.40 (d, 3H), 1.29 (s, 3H), 1.30 (d, 3H), 1.25 (m, 1H), 1.22 (d, 3H), 1.19 (d, 3H), 1.16 (d, 3H), 0.91 (t, 3H).

5 **Example 29**

**(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(5-(4-(pyridin-3-yl)-imidazol-1-yl)-pentylamido)-methylene]-erythromycin A**

To a solution of example 6 (0.100g) in anhydrous DMF (5mL) under nitrogen atmosphere intermediate 50 (0.048g), HATU (0.063g) and DIPEA (0.061mL) were sequentially added.

10 The reaction mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, the residue dissolved in DCM (30mL) and washed with water (25mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH 95/5, 90/10) to give a compound that was dissolved in MeOH (5mL) and stirred at room  
15 temperature overnight. Solvent evaporation under reduced pressure gave the title compound (0.090g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.98 (d, 1H), 8.45 (d, 1H), 8.09 (d, 1H), 7.55 (s, 1H), 7.34 (s, 1H), 7.29 (m, 1H), 6.45 (bd, 1H), 5.19 (dd, 1H), 4.82 (m, 1H), 4.29 (d, 1H), 4.12 (d, 1H), 3.98 (m, 2H), 3.80 (q, 1H), 3.55 (m, 1H), 3.17 (m, 1H), 3.06 (m, 2H), 2.55 (s+m, 1H + 3H), 2.45 (m, 1H),  
20 2.35 (m, 1H), 2.27 (s, 6H), 2.21 (m, 2H), 1.98 (m, 1H), 1.88 (m, 2H), 1.80 (m, 2H), 1.60-1.50 (m, 3H), 1.49 (s, 3H), 1.39 (d, 3H), 1.35 (m, 1H), 1.30 (d+s, 3H+3H), 1.23 (d, 3H), 1.16 (d, 3H+3H), 0.89 (t, 3H).

**Example 30**

25 **(11S,21R)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(4-(pyridin-3-yl)-imidazol-1-yl)-acetamido)-methylene]-erythromycin A**  
and

**Example 31**

30 **(11S,21S)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(4-(pyridin-3-yl)-imidazol-1-yl)-acetamido)-methylene]-erythromycin A**  
To a solution of example 6 (0.100g) in anhydrous DMF (8mL) under nitrogen atmosphere a solution of intermediate 47 (0.040g) in anhydrous DMF (2mL), HATU (0.057g) and DIPEA (0.060mL) were sequentially added. The mixture was stirred at room temperature for 8h. The solvent was evaporated under reduced pressure, the residue dissolved in DCM (30mL) and  
35 washed with water (2x10mL). The aqueous phase was extracted again with DCM (20mL). The organic layers were collected, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH from 95/5 to 92/8) to give the title compound 30 (0.008g) and the title compound 31 (0.021g).

40 TLC: DCM/MeOH 95/5 (R<sub>f</sub> (example 30) = 0.53)

TLC: DCM/MeOH 95/5 (R<sub>f</sub> (example 31) = 0.47).

**Example 32****(11S,21R)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(4-(pyridin-3-yl)-imidazol-1-yl)-acetamido)-methylene]-erythromycin A**

A solution of example 30 (0.007g) in MeOH (5mL) was stirred at room temperature for 48h.

- 5 After evaporating the solvent under reduced pressure, the crude material was purified by flash chromatography (eluting with: DCM\MeOH from 100\0 to 80\20) to give the title compound (0.003g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 9.19 (d, 1H), 8.98 (d, 1H), 8.47 (dd, 1H), 8.06 (d, 1H), 7.70 (d, 1H), 7.42 (d, 1H), 7.29 (m, 1H), 5.24 (d, 1H), 4.80 (dd, 1H), 3.18 (m, 1H), 2.94 (d, 1H), 0.99 (d, 3H).

10

**Example 33****(11S,21S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(4-(pyridin-3-yl)-imidazol-1-yl)-acetamido)-methylene]-erythromycin A**

A solution of example 31 (0.021g) in MeOH (5mL) was stirred at room temperature for 48h.

- 15 After evaporating the solvent under reduced pressure, the crude material was purified by flash chromatography (eluting with: DCM\MeOH from 100\0 to 80\20) to give the title compound (0.006g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.99 (d, 1H), 8.47 (d, 1H), 8.09 (d, 1H), 7.58 (s, 1H), 7.41 (s, 1H), 7.30 (m, 1H), 6.73 (d, 1H), 4.88 (dd, 1H), 4.67 (s, 1H), 3.08 (m, 1H), 2.41 (d, 1H), 1.16 (d, 3H).

20

**Example 34****(11S,21S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((quinolin-4-yl)carbonylamino)-methylene]-erythromycin A**

To a solution of example 6 (0.100g) in anhydrous DMF (8mL) under nitrogen atmosphere a solution of quinoline-4-carboxylic acid (0.026g) in anhydrous DMF (2mL), HATU (0.057g) and DIPEA (0.060mL) were added. The mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, the residue dissolved in DCM (30mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x10mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM\MeOH 94\6). The obtained compound was dissolved in MeOH (10mL) and stirred overnight. After solvent evaporation, purification by flash chromatography (eluting with: DCM\MeOH 90\10) gave the title compound (0.032g).

25

30

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.96 (d, 1H), 8.45 (d, 1H), 8.13 (d, 1H), 7.76 (t, 1H), 7.65 (t, 1H), 7.52 (d, 1H), 7.02 (d, 1H), 5.08 (dd, 1H), 3.17 (m, 1H), 2.60 (m, 1H), 1.28 (d, 3H).

35

**Example 35****(11S,21S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(quinolin-4-yl)-propionamido)-methylene]-erythromycin A**

To a solution of example 6 (0.100g) in anhydrous DMF (8mL) under nitrogen atmosphere 3-quinolin-4-yl-propionic acid (0.030g), HATU (0.057g) and DIPEA (0.060mL) were sequentially added. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, the residue dissolved in DCM (30mL) and

40

washed with water (25mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH 94/6) to give a compound that was dissolved in MeOH (2mL) and stirred at room temperature overnight. Solvent evaporation under reduced pressure gave the title compound (0.022g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.82 (d, 1H), 8.10 (d, 1H), 8.07 (d, 1H), 7.71 (t, 1H), 7.61 (t, 1H), 7.26 (d, 1H), 6.50 (bd, 1H), 5.14 (dd, 1H), 4.92 (dd, 1H), 4.28 (d, 1H), 4.12 (d, 1H), 3.80 (q, 1H), 3.54 (m, 1H), 3.46 (m, 2H), 3.16 (m, 1H), 3.08 (m, 1H), 3.04 (m, 1H), 2.60 (m, 2H), 2.49 (s, 3H), 2.45 (m, 1H), 2.39 (m, 1H), 2.26 (s, 6H), 2.00 (m, 1H), 1.80 (m, 2H), 1.72 (m, 1H), 1.65 (m, 1H), 1.60 (m, 1H), 1.50 (s, 3H), 1.39 (d, 3H), 1.29 (d, 3H), 1.28 (s, 3H), 1.25 (m, 1H), 1.24 (d, 3H), 1.18 (d, 3H), 1.14 (d, 3H), 0.91 (t, 3H).

#### **Example 36**

##### **(11S,21S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-quinolin-4-yl)-butyramido)-methylene]-erythromycin A**

To a solution of example 6 (0.075g) in anhydrous DMF (6mL) under nitrogen atmosphere intermediate **60** (0.027g), HATU (0.043g) and DIPEA (0.047mL) were sequentially added. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, the residue dissolved in DCM (20mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (15mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH from 97/3 to 95/5) to give a compound that was dissolved in MeOH (2mL) and stirred at room temperature overnight. Solvent evaporation under reduced pressure gave the title compound (0.039g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.81 (d, 1H), 8.11 (d, 1H), 8.09 (d, 1H), 7.69 (t, 1H), 7.58 (t, 1H), 7.26 (m, 1H), 6.47 (bd, 1H), 5.20 (dd, 1H), 4.88 (dd, 1H), 4.30 (d, 1H), 4.13 (s, 1H), 4.13 (m, 2H), 3.80 (q, 1H), 3.53 (m, 1H), 3.19-3.00 (m, 5H), 2.54 (s, 3H), 2.61-2.41 (m, 3H), 2.29 (s+m, 2H+ 6H), 2.11 (m, 2H), 2.00 (m, 1H), 1.80-1.60 (m, 7H), 1.39 (d, 3H), 1.29 (s+d, 3H+3H), 1.24 (m, 4H), 1.18 (d, 3H), 1.14 (d, 3H), 0.91 (t, 3H).

#### **Example 37**

##### **(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(5-quinolin-4-yl)-pentylamido)-methylene]-erythromycin A**

To a solution of example 6 (0.100g) in anhydrous DMF (6mL) under nitrogen atmosphere intermediate **62** (0.027g), HATU (0.057g) and DIPEA (0.057mL) were sequentially added. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, the residue dissolved in DCM (20mL) and washed with water (15mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH 95/5) to give a compound that was dissolved in MeOH (2mL) and stirred at room temperature overnight. Solvent evaporation under reduced pressure gave the title compound (0.024g).

1H-NMR (CDCl<sub>3</sub>) δ: 8.81 (d, 1H), 8.11 (d, 1H), 8.04 (m, 1H), 7.70 (m, 1H), 7.58 (m, 1H), 7.27 (m, 1H), 6.42 (bd, 1H), 5.18 (dd, 1H), 4.85 (dd, 1H), 4.30 (m, 1H), 4.13 (m, 1H), 3.79 (q, 1H), 3.54 (m, 1H), 3.17 (m, 1H), 3.08 (m, 4H), 2.58 (m, 1H), 2.55 (s, 3H), 2.45 (m, 1H), 2.40 (m, 1H), 2.27 (s, 6H), 2.23 (m, 2H), 1.98 (m, 1H), 1.81 (m, 4H), 1.75 (m, 1H), 1.70 (m, 1H), 1.65 (m, 1H), 1.60 (m, 1H), 1.50 (s, 3H), 1.40 (d, 3H), 1.30 (d, 3H), 1.28 (s, 3H), 1.24 (d, 3H), 1.20 (m, 1H), 1.18 (d, 3H), 1.14 (d, 3H), 0.89 (t, 3H).

#### Example 38

##### (11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(4-phenyl-imidazol-1-yl)-propionamido)-methylene]-erythromycin A

To a solution of example 7 (0.050g) in anhydrous DMF (4mL) under nitrogen atmosphere a solution of intermediate 65 (0.018g) in anhydrous DMF (1mL), HATU (0.013g) and DIPEA (0.013mL) were sequentially added. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, the residue dissolved in DCM (15mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (10mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH from 100/0 to 94/6) to give a compound that was dissolved in MeOH (2mL) and stirred at room temperature overnight. Evaporation of the solvent under reduced pressure gave the title compound (0.031g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.78 (d, 2H), 7.47 (d, 1H), 7.31 (t, 2H), 7.27 (d, 1H), 7.16 (t, 1H), 6.64 (d, 1H), 5.04 (dd, 1H), 4.99 (m, 1H), 4.20 (m, 1H), 3.01 (m, 1H), 2.60-2.50 (m, 2H), 2.33 (dd, 1H), 1.12 (d, 3H).

#### Example 39

##### (11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(4-phenyl-imidazol-1-yl)-acetamido)-methylene]-erythromycin A

To a suspension of intermediate 67 (0.022g) in anhydrous DMF (1.6mL) HATU (0.037g) and DIPEA (0.015mL) were sequentially added. The mixture was stirred under nitrogen atmosphere for 30min then example 7 (0.050g) was added. After stirring at room temperature overnight the reaction mixture was diluted with DCM (3.5mL), washed with a 5% NaHCO<sub>3</sub> aqueous solution (3mL) while ice-cooling and the aqueous phase extracted with DCM (2.5mL). The collected organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was dissolved in MeOH (10mL) and stirred at room temperature overnight. After solvent evaporation under reduced pressure the crude material was purified by flash chromatography (eluting with: DCM/MeOH/NH<sub>4</sub>OH from 100/0/0 to 94/6/0.5) to give the title compound (0.010g).

1H-NMR (DMSO) δ: 8.62 (d, 1H), 7.71 (d, 2H), 7.58 (d, 1H), 7.49 (d, 1H), 7.33 (t, 2H), 7.17 (t, 1H), 4.69 (d, 1H), 4.62 (d, 1H), 4.59 (d, 1H), 3.19 (m, 1H), 2.59 (m, 1H), 1.10 (d, 3H).

#### Example 40

##### (11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(4-thiophen-2-yl-imidazol-1-yl)-propionamido)-methylene]-erythromycin A

To a solution of example 7 (0.034g) in anhydrous DMF (4mL) under nitrogen atmosphere a solution of intermediate **69** (0.012g) in anhydrous DMF (1mL), HATU (0.019g) and DIPEA (0.020mL) were sequentially added. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, the residue dissolved in DCM (10mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (5mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH from 100/0 to 94/6) to give a compound that was dissolved in MeOH (5mL) and stirred at room temperature overnight. Solvent evaporation under reduced pressure gave the title compound (0.020g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.46 (d, 1H), 7.31 (dd, 1H), 7.20 (d, 1H), 7.14 (dd, 1H), 7.00 (dd, 1H), 6.68 (d, 1H), 5.08 (dd, 1H), 4.40 (m, 1H), 4.20 (m, 1H), 3.05 (m, 1H), 2.68 (m, 1H), 2.50 (m, 1H), 2.38 (dd, 1H), 1.16 (d, 3H).

#### Example 41

#### (11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-[3-(1,3-thiazol-2-yl)-1*H*-pyrazol-1-yl]propionamido)-methylene]-erythromycin A

To a solution of example 7 (0.050g) in anhydrous DMF (4mL) under nitrogen atmosphere a solution of intermediate **70** (0.017g) in anhydrous DMF (1mL), HATU (0.029g) and DIPEA (0.030mL) were sequentially added. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, the residue dissolved in DCM (10mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (5mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH from 100/0 to 95/5) to give a compound that was dissolved in MeOH (3mL) and stirred at room temperature overnight. Solvent evaporation under reduced pressure and purification by flash chromatography (eluting with: DCM/MeOH from 100/0 to 95/5) gave the title compound (0.007g).

$m/z$  ([MH]<sup>+</sup>) = 832.

#### Example 42

#### (11*S*,21*R*,*S*)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2*S*)-*tert*-butoxycarbonylamino-3-(1*H*-indol-3-yl)-propionamido)-methylene]-erythromycin A

To a solution of example 6 (0.050g) in anhydrous DMF (4mL) under nitrogen atmosphere (2*S*)-*tert*-butoxycarbonylamino-3-(1*H*-indol-3-yl)-propionic acid (0.027g), HATU (0.031g) and DIPEA (0.031mL) were sequentially added. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, the residue dissolved in DCM (10mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (5mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH from 98/2 to 97/3) to give the title compound (0.043g).

$m/z$  ([MH]<sup>+</sup>) = 955.



**Example 43****(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2S)-tert-butoxycarbonylamino-3-(1H-indol-3-yl)-propionamido)-methylene]-erythromycin A**

A solution of example 42 (0.013g) in MeOH (2mL) was stirred at room temperature overnight. Solvent evaporation under reduced pressure gave the title compound (0.010g).  
m/z ([MH]<sup>+</sup>) = 913.

**Example 44****(11S,21S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2S)-2-amino-3-(1H-indol-3-yl)-propionamido)-methylene]-erythromycin A**

To a solution of example 42 (0.025g) in anhydrous DCM (0.5mL) cooled to 0°C trifluoroacetic acid (0.1mL) was added. After removing the ice-bath, the reaction mixture was stirred at room temperature for 1h. The mixture was concentrated under reduced pressure, the residue dissolved in DCM (5mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2mL). The aqueous phase was extracted with DCM (3x3mL). The collected organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH 97/3) to give a compound that was dissolved in MeOH (1mL) and the solution was stirred at room temperature overnight. Solvent evaporation under reduced pressure gave the title compound (0.004g).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.12 (bs, 1H), 8.06 (d, 1H), 7.65 (d, 1H), 7.36 (d, 1H), 7.19 (t, 1H), 7.16 (d, 1H), 7.13 (t, 1H), 5.35 (dd, 1H), 4.75 (dd, 1H), 3.70 (dd, 1H), 3.34 (dd, 1H), 3.09-3.04 (m, 3H), 2.46-2.44 (m, 2H), 1.20 (d, 3H).  
m/z ([MH]<sup>+</sup>) = 813.

**Example 45****(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(quinoxalin-2-ylsulfanyl)-acetamido)-methylene]-erythromycin A**

To a solution of (quinoxalin-2-ylsulfanyl)-acetic acid (0.095g) in anhydrous DMF (8.3mL) under nitrogen atmosphere HATU (0.164g) and DIPEA (0.089mL) were added. The reaction mixture was stirred at room temperature for 30min then example 6 (0.262g) was added. The reaction mixture was stirred at room temperature for 20h then it was diluted with DCM (30mL) and washed with a 5% NaHCO<sub>3</sub> aqueous solution (20mL). The aqueous phase was extracted with DCM (25mL), the collected organic layers were washed with a 5% NaHCO<sub>3</sub> aqueous solution (20mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was dissolved in MeOH (10mL) and stirred at room temperature overnight. After evaporating the solvent the crude material was purified by flash chromatography (eluting with: DCM/MeOH/NH<sub>4</sub>OH from 100/0 to 93/7/1) to give the title compound (0.199g).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.67 (s, 1H), 8.19 (dd, 1H), 8.04 (dd, 1H), 7.90 (d, 1H), 7.74 (dt, 1H), 7.66 (dt, 1H), 5.20 (dd, 1H), 4.67 (dd, 1H), 4.30 (d, 1H), 4.06 (m+d, 1H+1H), 3.95 (d, 1H), 3.73 (q, 1H), 3.52 (m, 2H), 3.16 (dd, 1H), 3.06-3.0 (m, 2H), 2.52 (s, 3H), 2.50-2.40 (m, 2H), 2.42 (dd, 1H), 2.27 (s, 6H), 1.92 (m, 1H), 1.81-1.65 (m, 2H), 1.66 (m, 1H), 1.51 (m, 1H), 1.47

(s, 3H), 1.36 (d, 3H), 1.27 (d, 3H), 1.24 (m, 1H), 1.24 (d, 3H), 1.23 (s, 3H), 1.12 (d, 3H), 1.06 (d, 3H), 0.81 (t, 3H).

#### **Example 46**

##### **(11*S*,21*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(quinoxalin-2-ylsulfanyl)-acetamido)-methylene]-erythromycin A**

To a solution of (quinoxalin-2-ylsulfanyl)-acetic acid (0.395g) in anhydrous DMF (5mL) under nitrogen atmosphere and HATU (0.682g) and DIPEA (0.365mL) were added at room temperature. The reaction mixture was stirred at room temperature for 30min then a solution of example 7 (1.0g) in anhydrous DMF (3mL) was added. The reaction mixture was stirred at room temperature for 3h then it was poured into a 5% NaHCO<sub>3</sub> aqueous solution (30mL) and the solution extracted with Et<sub>2</sub>O (2x30mL). The collected organic layers were washed with brine (30mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was dissolved in MeOH (25mL) and stirred at room temperature overnight. After evaporating the solvent the crude material was purified by flash chromatography (eluting with: DCM\MeOH\NH<sub>4</sub>OH from 100\0\0 to 93\7\0.2). Crystallisation from EtOAc gave the title compound (0.454g, (21*S*) isomer 99% pure by NMR analysis).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.67 (s, 1H), 8.19 (dd, 1H), 8.04 (dd, 1H), 7.90 (d, 1H), 7.74 (dt, 1H), 7.66 (dt, 1H), 5.20 (dd, 1H), 4.67 (dd, 1H), 4.30 (d, 1H), 4.06 (m+d, 1H+1H), 3.95 (d, 1H), 3.73 (q, 1H), 3.52 (m, 2H), 3.16 (dd, 1H), 3.06-3.0 (m, 2H), 2.52 (s, 3H), 2.50-2.40 (m, 2H), 2.42 (dd, 1H), 2.27 (s, 6H), 1.92 (m, 1H), 1.81-1.65 (m, 2H), 1.66 (m, 1H), 1.51 (m, 1H), 1.47 (s, 3H), 1.36 (d, 3H), 1.27 (d, 3H), 1.24 (m, 1H), 1.24 (d, 3H), 1.23 (s, 3H), 1.12 (d, 3H), 1.06 (d, 3H), 0.81 (t, 3H).

#### **Example 47**

##### **(11*S*,21*R,S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-4-oxo)-butyramido)-methylene]-erythromycin A**

To a solution of 4-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-4-oxo-butyric acid (0.1165g) in anhydrous DMF (9.5mL) under nitrogen atmosphere HATU (0.188g) and DIPEA (0.102mL) were added. The reaction mixture was stirred at room temperature for 30min then example 7 (0.300g) was added. The reaction mixture was stirred at room temperature for 20h then it was diluted with DCM (30mL) and washed with a 5% NaHCO<sub>3</sub> aqueous solution (20mL). The aqueous phase was extracted with DCM (25mL), the collected organic layers were washed with a 5% NaHCO<sub>3</sub> aqueous solution (20mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was dissolved in MeOH (10mL) and stirred at room temperature overnight. After evaporating the solvent the crude material was purified by flash chromatography (eluting with: DCM\MeOH\NH<sub>4</sub>OH from 100\0\0 to 93\7\1) to give the title compound (0.170g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.52 (d, 2H), 6.89 (d, 1H), 6.73 (d, NH), 5.20 (dd, 1H), 4.84 (dd, 1H), 4.35-4.25 (m, 5H), 4.13 (d, 1H), 3.80 (q, 1H), 3.60-3.55 (m, 2H), 3.32-3.22 (m, 2H), 3.18 (dd, 1H), 3.10-3.00 (m, 2H), 2.65-2.55 (m, 2H), 2.60 (s, 3H), 2.44 (m, 2H), 2.27 (s, 6H), 2.27 (m, 1H), 1.99 (m, 1H), 1.80 (dd, 1H), 1.75 (m, 1H), 1.68 (m, 1H), 1.60 (m, 1H), 1.50 (s, 3H), 1.40

(d, 3H), 1.32 (s, 3H), 1.30 (d, 3H), 1.25 (m, 1H), 1.24 (d, 3H), 1.19 (d, 3H), 1.17 (d, 3H), 0.93 (t, 3H).

#### **Example 48**

5 **(11*S*,21*R,S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(4-oxo-4,5,6,7-tetrahydro-benzo[*b*]thiophen-2-yl)-4-oxo-butyramido)-methylene]-erythromycin A**

To a solution of 4-(4-oxo-4,5,6,7-tetrahydro-benzo[*b*]thiophen-2-yl)-4-oxo-butyric acid (0.013g) in anhydrous DMF (0.850mL) under nitrogen atmosphere and HATU (0.019g) and DIPEA (0.010mL) were added. The reaction mixture was stirred at room temperature for 30min then example 6 (0.028g) was added. The reaction mixture was stirred at room temperature for 2.5h then it was diluted with DCM (2mL) and washed with a 5% NaHCO<sub>3</sub> aqueous solution (2mL). The aqueous phase was extracted with DCM (1.5mL), the collected organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was dissolved in MeOH (5mL) and stirred at room temperature for 24h. After evaporating the solvent the crude material was purified by flash chromatography (eluting with: DCM/MeOH/NH<sub>4</sub>OH from 100/0/0 to 92/8/0.2) to give the title compound (0.031g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.02 (s, 1H), 6.68 (d, NH), 5.13 (dd, 1H), 4.88 (dd, 1H), 4.32 (d, 1H), 4.14(d, 1H), 3.81 (q, 1H), 3.55 (m, 1H), 3.28 (m, 2H), 3.21 (m, 1H), 3.09-3.03 (m, 4H), 2.62 (s, 3H), 2.63-2.57 (m, 6H), 2.46 (dd, 1H), 2.35 (s, 6H), 2.24 (m, 2H), 1.98 (m, 1H), 1.80-1.70 (m, 3H), 1.60 (m, 1H), 1.49 (s, 3H), 1.40 (d, 3H), 1.32 (s, 3H), 1.29 (d, 3H), 1.25 (m, 4H), 1.18 (d, 3H), 1.17 (d, 3H), 0.92 (t, 3H).

#### **Example 49**

25 **(11*S*,21*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(4-oxo-4,5,6,7-tetrahydro-benzo[*b*]thiophen-2-yl)-4-oxo-butyramido)-methylene]-erythromycin A**

To a solution of 4-(4-oxo-4,5,6,7-tetrahydro-benzo[*b*]thiophen-2-yl)-4-oxo-butyric acid (1.280g) in anhydrous DMF (12mL) under nitrogen atmosphere HATU (2.02g) and DIPEA (1.06mL) were added. The reaction mixture was stirred at room temperature for 30min then a solution of example 7 (2.90g) in anhydrous DMF (10mL) was added. The reaction mixture was stirred at room temperature overnight then it was diluted with EtOAc (100mL) and washed with a 5% NaHCO<sub>3</sub> aqueous solution (2x50mL) and brine (50mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH from 100/0 to 98/2) to give a compound that was dissolved in MeOH (150mL) and stirred overnight. After evaporating the solvent the residue was purified by flash chromatography (eluting with: DCM/MeOH from 100/0 to 97/3) to give the title compound (2.40g, (21*S*) isomer 95% pure by NMR analysis).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.02 (s, 1H), 6.68 (d, NH), 5.13 (dd, 1H), 4.88 (dd, 1H), 4.32 (d, 1H), 4.14(d, 1H), 3.81 (q, 1H), 3.55 (m, 1H), 3.28 (m, 2H), 3.21 (m, 1H), 3.09-3.03 (m, 4H), 2.62 (s, 3H), 2.63-2.57 (m, 6H), 2.46 (dd, 1H), 2.35 (s, 6H), 2.24 (m, 2H), 1.98 (m, 1H), 1.80-1.70

(m, 3H), 1.60 (m, 1H), 1.49 (s, 3H), 1.40 (d, 3H), 1.32 (s, 3H), 1.29 (d, 3H), 1.25 (m, 4H), 1.18 (d, 3H), 1.17 (d, 3H), 0.92 (t, 3H).

#### **Example 50**

5 **(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(4-methoxy-3-nitro-phenyl)-4-oxo-butyramido)-methylene]-erythromycin A**

To a solution of 4-(4-methoxy-3-nitro-phenyl)-4-oxo-butyric acid (0.136g) in anhydrous DMF (9mL) under nitrogen atmosphere HATU (0.205g) and DIPEA (0.110mL) were added. The reaction mixture was stirred at room temperature for 30min then example 6 (0.300g) was added. The reaction mixture was stirred at room temperature for 2.5h then it was diluted with DCM (21mL) and washed with a 5% NaHCO<sub>3</sub> aqueous solution (18mL). The aqueous phase was extracted with DCM (15mL), the collected organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was dissolved in MeOH (30mL) and DCM (2mL) and stirred at room temperature for 48h. After evaporating the solvent the crude material was purified by LC (mobile phase: A\B 85\15 for 1min, from 85\15 to 15\85 in 20min; λ= 255nm) to give the title compound (0.149g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.47 (d, 1H), 8.19 (dd, 1H), 7.15 (d, 1H), 6.69 (d, NH), 5.18 (dd, 1H), 4.85 (dd, 1H), 4.31 (d, 1H), 4.14 (d, 1H), 4.04 (s, 3H), 3.80 (q, 1H), 3.54 (m, 1H), 3.32 (m, 2H), 3.18 (dd, 1H), 3.06-3.0 (m, 2H), 2.66 (m, 2H), 2.60 (s, 3H), 2.46 (m, 1H), 2.42 (dd, 1H), 2.28 (s, 6H), 1.98 (m, 1H), 1.81-1.55 (m, 4H), 1.49 (s, 3H), 1.40 (d, 3H), 1.32 (s, 3H), 1.30 (d, 3H), 1.25 (d, 3H), 1.25 (m, 1H), 1.18 (d, 3H), 1.17 (d, 3H), 0.81 (t, 3H).

#### **Example 51**

25 **(11*S*,21*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(4-methoxy-3-nitro-phenyl)-4-oxo-butyramido)-methylene]-erythromycin A**

To a solution of 4-(4-methoxy-3-nitro-phenyl)-4-oxo-butyric acid (2.782g) in anhydrous DMF (36mL) under nitrogen atmosphere HATU (1.230g) and DIPEA (0.656mL) were added. The reaction mixture was stirred at room temperature for 30min then example 7 (1.8g) was added. The reaction mixture was stirred at room temperature for 3h then it was diluted with Et<sub>2</sub>O (200mL) and washed with a 5% NaHCO<sub>3</sub> aqueous solution (2x100mL). The aqueous phase was extracted with Et<sub>2</sub>O (50mL) and DCM (50mL), the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH from 100\0 to 96\4). The obtained compound was dissolved in MeOH (100mL) and stirred at room temperature overnight. After evaporating the solvent the product was purified by flash chromatography (eluting with: DCM/MeOH from 100\0 to 96\4) to give the title compound (1.510g, (21*S*) isomer 95% pure by NMR analysis).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.47 (d, 1H), 8.19 (dd, 1H), 7.15 (d, 1H), 6.69 (d, NH), 5.18 (dd, 1H), 4.85 (dd, 1H), 4.31 (d, 1H), 4.14 (d, 1H), 4.04 (s, -OCH<sub>3</sub>), 3.80 (q, 1H), 3.54 (m, 1H), 3.32 (m, 2H), 3.18 (dd, 1H), 3.06-3.0 (m, 2H), 2.66 (m, 2H), 2.60 (s, 3H), 2.46 (m, 1H), 2.42 (dd, 1H), 2.28 (s, 6H), 1.98 (m, 1H), 1.81-1.55 (m, 4H), 1.49 (s, 3H), 1.40 (d, 3H), 1.32 (s, 3H), 1.30 (d, 3H), 1.25 (d, 3H), 1.25 (m, 1H), 1.18 (d, 3H), 1.17 (d, 3H), 0.81 (t, 3H).

**Example 52****(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(2-hydroxy-4,5-dimethoxy-phenyl)-4-oxo-butyramido)-methylene]-erythromycin A**

5 To a solution of 4-(2-hydroxy-4,5-dimethoxy-phenyl)-4-oxo-butyric acid (0.137g) in anhydrous DMF (9mL) under nitrogen atmosphere HATU (0.205g) and DIPEA (0.110mL) were added. The reaction mixture was stirred at room temperature for 30min then example 6 (0.300g) was added. The reaction mixture was stirred at room temperature for 2.5h then it was diluted with DCM (21mL) and washed with a 5% NaHCO<sub>3</sub> aqueous solution (18mL). The aqueous phase was extracted with DCM (15mL), the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure.

10 The residue was dissolved in MeOH (10mL) and stirred at room temperature for 24h. After evaporating the solvent the crude material was purified by LC (mobile phase: A\B from 85\15 to 15\85 in 20 min;  $\lambda = 237\text{nm}$ ) to give the title compound (0.120g).

15 <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 12.49 (s, 1H), 7.14 (s, 1H), 6.71 (d, NH), 6.44 (s, 1H), 5.18 (dd, 1H), 4.88 (dd, 1H), 4.31 (d, 1H), 4.14 (d, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.80 (q, 1H), 3.55 (m, 1H), 3.41-3.30 (m, 2H), 3.20 (dd, 1H), 3.11-3.0 (m, 2H), 2.70-2.60 (m, 2H), 2.61 (s, 3H), 2.52 (m, 1H), 2.43 (dd, 1H), 2.31 (s, 6H), 1.98-1.70 (m, 3H), 1.60 (m, 1H), 1.50 (s, 3H), 1.30 (d, 3H), 1.26 (d, 3H), 1.25 (m, 1H), 1.24 (d+d, 6H), 1.19 (d, 3H), 1.17 (d, 3H), 0.91 (t, 3H).

20

**Example 53****(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(3-hydroxy-4-methoxy-phenyl)-4-oxo-butyramido)-methylene]-erythromycin A**

25 To a solution of 4-(3-hydroxy-4-methoxy-phenyl)-4-oxo-butyric acid (0.121g) in anhydrous DMF (9mL) under nitrogen atmosphere HATU (0.205g) and DIPEA (0.110mL) were added. The reaction mixture was stirred at room temperature for 30min then example 6 (0.300g) was added. The reaction mixture was stirred at room temperature for 2.5h then it was diluted with DCM (21mL) and washed with a 5% NaHCO<sub>3</sub> aqueous solution (18mL). The aqueous phase was extracted with DCM (15mL), the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was dissolved in MeOH (30mL) and DCM (2mL) and stirred at room temperature for 48h. After evaporating the solvent the crude material was purified by LC (mobile phase: A\B 85\15 for 1min, from 85\15 to 15\85 in 20 min;  $\lambda = 230\text{nm}$ ) to give the title compound (0.020g).

30 <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 7.57 (m, 2H), 6.89 (d, 1H), 6.71 (d, 1H), 5.88 (bs, 1H), 5.22 (dd, 1H), 4.81 (dd, 1H), 4.31 (d, 1H), 4.13 (d, 1H), 3.96 (s, 3H), 3.81 (q, 1H), 3.55 (m, 1H), 3.31 (m, 2H), 3.22 (m, 1H), 3.09-3.04 (m, 2H), 2.66-2.54 (m, 4H), 2.61 (s, 3H), 2.44 (dd, 1H), 2.34 (s, 6H), 2.00 (m, 1H), 1.81-1.70 (m, 3H), 1.6 (m, 1H), 1.50 (s, 3H), 1.41 (d, 3H), 1.31 (s, 3H), 1.29 (d, 3H), 1.25 (d, 3H), 1.25 (m, 1H), 1.19 (d, 3H), 1.17 (d, 3H), 0.93 (t, 3H).

40 **Example 54**

**(11S,21S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(3-hydroxy-4-methoxy-phenyl)-4-oxo-butyramido)-methylene]-erythromycin A**

To a solution of 4-(3-hydroxy-4-methoxy-phenyl)-4-oxo-butyric acid (0.273g) in anhydrous DMF (3.5mL), HOBt (0.165g) and EDC (0.234g) were added under nitrogen atmosphere. After stirring 5min example 7 (0.627g) was added, and the resulting mixture was stirred at room temperature for 3h. The reaction mixture was diluted with DCM (15mL) washed with a 5% NaHCO<sub>3</sub> aqueous solution (10mL). The organic layer was washed with brine (10ml), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH from 97/3 to 95/5) to give a compound that was dissolved in MeOH (10mL) and stirred at room temperature overnight. After solvent evaporation the compound was purified by preparative LC (column Waters XTerra MS C18 (19 x 300mm, 7µm); flow rate = 12 ml/min, A/B from 70/30 to 10/90 in 25min; λ= 230nm) to give the title compound (0.165g, (21*S*) isomer 94% pure by NMR analysis).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.57 (m, 2H), 6.89 (d, 1H), 6.71 (d, 1H), 5.88 (bs, 1H), 5.22 (dd, 1H), 4.81 (dd, 1H), 4.31 (d, 1H), 4.13 (d, 1H), 3.96 (s, 3H), 3.81 (q, 1H), 3.55 (m, 1H), 3.31 (m, 2H), 3.22 (m, 1H), 3.09-3.04 (m, 2H), 2.66-2.54 (m, 4H), 2.61 (s, 3H), 2.44 (dd, 1H), 2.34 (s, 6H), 2.00 (m, 1H), 1.81-1.70 (m, 3H), 1.6 (m, 1H), 1.50 (s, 3H), 1.41 (d, 3H), 1.31 (s, 3H), 1.29 (d, 3H), 1.25 (d, 3H), 1.25 (m, 1H), 1.19 (d, 3H), 1.17 (d, 3H), 0.93 (t, 3H).

#### **Example 55**

#### **(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(3,4-dimethoxy-phenyl)-4-oxo-butyramido)-methylene]-erythromycin A**

To a solution of 4-(3,4-dimethoxy-phenyl)-4-oxo-butyric acid (0.128g) in anhydrous DMF (9mL) under a nitrogen atmosphere HATU (0.205g) and DIPEA (0.110mL) were added. The reaction mixture was stirred at room temperature for 30min then example 6 (0.300g) was added. The reaction mixture was stirred at room temperature for 2.5h then it was diluted with DCM (21mL) and washed with a 5% NaHCO<sub>3</sub> aqueous solution (18mL). The aqueous phase was extracted with DCM (15mL), the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was dissolved in MeOH (30mL) and stirred at room temperature for 24h. After evaporating the solvent the crude material was purified by flash chromatography (eluting with: DCM/MeOH/NH<sub>4</sub>OH from 100/0/0 to 92/8/0.2) to give the title compound (0.293g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.95 (d, NH), 7.70 (dd, 1H), 7.55 (d, 1H), 6.99 (d, 1H), 5.30 (dd, 1H), 5.30 (dd, 1H), 4.71 (m, 1H), 4.37 (d, 1H), 4.08 (d, 1H), 3.96-3.93 (m, 4H), 3.90 (q, 1H), 3.68 (m, 1H), 3.39 (dd, 1H), 3.34 (m, 2H), 3.19 (m, 1H), 3.14 (m, 1H), 2.75 (s, 6H), 2.66-2.61 (m, 6H), 2.49 (d, 1H), 1.99-1.96 (m, 2H), 1.84-1.71 (m, 2H), 1.64 (m, 1H), 1.56 (s, 3H), 1.41 (m+d, 1H+3H), 1.32 (d, 3H), 1.31 (s, 3H), 1.26 (d, 3H), 1.23 (d, 3H), 1.21 (d, 3H), 0.95 (t, 3H).

#### **Example 56**

#### **(11*S*,21*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(3,4-dimethoxy-phenyl)-4-oxo-butyramido)-methylene]-erythromycin A**

To a solution of 4-(3,4-dimethoxy-phenyl)-4-oxo-butyric acid (0.695g) in anhydrous DMF (15mL) under nitrogen atmosphere HATU (1.08g) and DIPEA (0.586mL) were added. The

reaction mixture was stirred at room temperature for 30min then example 7 (1.50g) was added. The reaction mixture was stirred at room temperature for 18h then it was diluted with DCM (35mL) and washed with a 5% NaHCO<sub>3</sub> aqueous solution (30mL). The aqueous phase was extracted with DCM (25mL), the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was dissolved in MeOH (50mL) and stirred at room temperature for 18h. After evaporating the solvent the crude material was crystallised from DCM to give the title compound (1.26g, (21*S*) isomer 98% pure by NMR analysis).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.95 (d, NH), 7.70 (dd, 1H), 7.55 (d, 1H), 6.99 (d, 1H), 5.30 (dd, 1H), 5.30 (dd, 1H), 4.71 (m, 1H), 4.37 (d, 1H), 4.08 (d, 1H), 3.96-3.93 (m, 4H), 3.90 (q, 1H), 3.68 (m, 1H), 3.39 (dd, 1H), 3.34 (m, 2H), 3.19 (m, 1H), 3.14 (m, 1H), 2.75 (s, 6H), 2.66-2.61 (m, 6H), 2.49 (d, 1H), 1.99-1.96 (m, 2H), 1.84-1.71 (m, 2H), 1.64 (m, 1H), 1.56 (s, 3H), 1.41 (m+d, 1H+3H), 1.32 (d, 3H), 1.31 (s, 3H), 1.26 (d, 3H), 1.23 (d, 3H), 1.21 (d, 3H), 0.95 (t, 3H).

#### **Example 57**

##### **(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(4-hydroxy-3-methoxy-phenyl)-4-oxo-butylamido)-methylenel]-erythromycin A**

To a solution of 4-(4-hydroxy-3-methoxy-phenyl)-4-oxo-butyric acid (0.922g) in anhydrous DMF (20mL) HOBt (0.656g) and EDC (0.933g) were added. Then example 6 (2.5g) was added, and the resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with DCM (75mL) washed with a 1N HCl aqueous solution (30mL) then with a saturated NaHCO<sub>3</sub> aqueous solution (30mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH 98/2) then dissolved in MeOH (10mL) and stirred at room temperature overnight. Solvent evaporation gave the title compound (0.600g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.57 (dd, 1H), 7.50 (d, 1H), 6.92 (d, 1H), 6.89 (d, 1H), 6.05 (bs, 1H), 5.19 (dd, 1H), 4.80 (dd, 1H), 4.28 (d, 1H), 4.10 (d, 1H), 3.93 (s, 3H), 3.77 (q, 1H), 3.58 (bs, 1H), 3.51 (m, 1H), 3.30 (m, 2H), 3.17 (dd, 1H), 3.06 (m, 1H), 3.02 (m, 1H), 2.6 (m, 3H), 2.57 (s, 3H), 2.48 (bm, 1H), 2.41 (dd, 1H), 2.28 (bs, 6H), 1.95 (m, 1H), 1.81-1.50 (m, 4H), 1.47 (s, 3H), 1.37 (d, 3H), 1.28 (s, 3H), 1.27 (d, 4H), 1.22 (d, 3H), 1.17 (d, 3H), 1.15 (d, 3H), 0.90 (t, 3H).

#### **Example 58**

##### **(11*S*,21*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(4-hydroxy-3-methoxy-phenyl)-4-oxo-butylamido)-methylenel]-erythromycin A**

To a solution of 4-(4-hydroxy-3-methoxy-phenyl)-4-oxo-butyric acid (0.720g) in anhydrous DMF (12mL) HOBt (0.259g) and EDC (0.368g) were added under nitrogen atmosphere. Then example 7 (1.65g) was added, and the resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with DCM (50mL) washed with a 1N HCl aqueous solution (20mL) then with a saturated NaHCO<sub>3</sub> aqueous solution (20mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH 98/2) then

dissolved in MeOH (10mL) and stirred at room temperature overnight. Solvent evaporation gave the title compound (0.360g, (21*S*) isomer 95% pure by NMR analysis).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.57 (dd, 1H), 7.50 (d, 1H), 6.92 (d, 1H), 6.89 (d, 1H), 6.05 (bs, 1H), 5.19 (dd, 1H), 4.80 (dd, 1H), 4.28 (d, 1H), 4.10 (d, 1H), 3.93 (s, 3H), 3.77 (q, 1H), 3.58 (bs, 1H), 3.51 (m, 1H), 3.30 (m, 2H), 3.17 (dd, 1H), 3.06 (m, 1H), 3.02 (m, 1H), 2.6 (m, 3H), 2.57 (s, 3H), 2.48 (bm, 1H), 2.41 (dd, 1H), 2.28 (bs, 6H), 1.95 (m, 1H), 1.81-1.50 (m, 4H), 1.47 (s, 3H), 1.37 (d, 3H), 1.28 (s, 3H), 1.27 (d, 4H), 1.22 (d, 3H), 1.17 (d, 3H), 1.15 (d, 3H), 0.90 (t, 3H).

10 **Example 59**

**(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(3-methoxy-quinoxalin-2-ylsulfanyl)-acetamido)-methylene]-erythromycin A**

To a solution of intermediate **72** (0.032g) in anhydrous DMF (2mL) HATU (0.048g) and DIPEA (0.022mL) were added under nitrogen atmosphere. After stirring for 45min example **7** (0.070g) was added and the mixture stirred overnight. Water (5mL) was added and the solution extracted with DCM (2x10mL). The organic phase was washed with brine (5mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was dissolved in MeOH (5mL) and stirred overnight. The crude material was purified by flash chromatography (eluting with: DCM/MeOH 94/6) to give the title compound (0.060g).

20 m/z ([MH]<sup>+</sup>) = 859

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.09 (d, 1H), 7.78 (d, 1H), 7.81 (d, 1H), 7.56 (t, 1H), 7.53 (t, 1H), 4.65 (t, 1H), 4.15 (s, 3H), 4.06 (d, 1H), 3.90 (d, 1H), 3.03 (m, 1H), 2.42 (m, 1H), 1.10 (d, 3H).

**Example 60**

25 **(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(quinoxalin-2-yloxy)-acetamido)-methylene]-erythromycin A**

To a solution of intermediate **74** (0.038g) in anhydrous DMF (1.5mL) HATU (0.072g) and DIPEA (0.033mL) were added under nitrogen atmosphere. After stirring for 45min example **7** (0.090g) was added and the mixture stirred overnight. Water (8mL) was added and the solution extracted with DCM (2x15mL). Collected organic phases were washed with a saturated NaHCO<sub>3</sub> aqueous solution (10mL), brine (10mL), then dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was dissolved in MeOH (5mL) and stirred overnight. Purification of the crude material by flash chromatography (eluting with: DCM/MeOH 95/5) gave the title compound (0.047g).

35 m/z ([MH]<sup>+</sup>) = 813

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.35 (s, 1H), 7.86 (d, 1H), 7.57 (td, 1H), 7.36 (m, 2H), 7.26 (d, 1H), 5.10 (dd, 1H), 5.02 (d, 1H), 4.87 (d, 1H), 3.01 (m, 1H), 2.34 (m, 1H), 1.11 (d, 3H).

**Example 61**

40 **(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(3-amino-4-methoxy-phenyl)-4-oxo-butyramido)-methylene]-erythromycin A**



To a solution of example **51** (0.070g) in anhydrous MeOH (5mL) palladium (10wt. % on carbon powder, 0.050g) was added and the mixture stirred under hydrogen atmosphere (1 atm) for 1hr. Filtration through a silica pad eluting with MeOH and purification by preparative TLC (eluting with: DCM\MeOH 90\10) gave the title compound (0.008g).

- 5 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.47 (d, 1H), 8.19 (d, 1H), 7.15 (d, 1H), 6.68 (d, 1H), 4.82 (d, 1H), 4.04 (s, 3H), 3.32 (t, 2H), 3.07 (m, 1H), 2.70-2.60 (m, 2H), 2.39 (m, 1H), 2.08 (s, 3H), 1.11 (d, 3H)

#### **Example 62**

##### **(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-hydroxyimino-4-(4-methoxy-3-nitro-phenyl)-butyramido)-methylene]-erythromycin A**

- 10 To a solution of example **51** (0.050g) in anhydrous MeOH (1mL) hydroxylamine hydrochloride (0.050g) and ammonium acetate (0.100g) were added. The reaction mixture was stirred at 60°C for 3h. After solvent evaporation, the crude material was purified by flash chromatography (eluting with: DCM\MeOH 90\10) to give the title compound (0.015g).

- 15 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.17 (d, 1H), 7.82 (dd, 1H), 7.13 (d, 1H), 6.58 (bm, 1H), 4.80 (m, 1H), 3.00 (m, 1H), 3.10 (m, 2H), 2.50 (m, 2H), 2.34 (m, 1H), 1.14 (d, 3H).

#### **Example 63**

##### **(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-quinoxaline-2-sulfonyl)-acetamido)-methylene]-erythromycin A**

- 20 To a solution of example **46** (0.050g) in a 1\1 mixture of water\DCM (4mL) magnesium monoperoxyphthalate (0.040g) was added. After stirring for 24h the aqueous phase was extracted with DCM (3x5mL), the organic extracts washed with a 5% Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub> aqueous solution (5mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was dissolved in THF (1mL), polystyrene triphenylphosphine resin (0.050g) was added and the mixture heated to 65°C for 2h. After cooling to room temperature, the mixture was filtered and concentrated to give the title compound (0.050g).

- 25 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 9.52 (s, 1H), 8.24 (m, 1H), 8.00-7.80 (m, 2H), 7.70 (bm, 1H), 4.83 (m, 1H), 4.49 (d, 1H), 4.04 (d, 1H), 3.06 (m, 1H), 2.50 (m, 1H), 1.15 (d, 3H).

30

#### **Example 64**

##### **(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-phenyl-propylamino)-methylene]-erythromycin A**

- 35 A solution of example **6** (0.045g) and 3-phenyl propionaldehyde (0.010mL) in anhydrous MeOH (1mL) was stirred at room temperature for 1h under nitrogen atmosphere. Then sodium cyanoborohydride (0.007g) and acetic acid (0.004mL) were added. The mixture was stirred at room temperature for 1h then the reaction was quenched with a saturated NaHCO<sub>3</sub> aqueous solution (2mL). After solvent evaporation, the aqueous phase was extracted with DCM (3x10mL), the organic layer dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was dissolved in MeOH (1mL) and stirred at room temperature overnight. After evaporating the solvent the crude material was purified by flash chromatography (eluting with: DCM \MeOH 95\5) to give the title compound (0.039g).
- 40

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.40-7.00 (m, 5H), 5.74 (dd, 1H), 4.31 (d, 1H), 4.25 (d, 1H), 4.13 (s, 1H), 3.84 (q, 1H), 3.54 (m, 1H), 3.18 (m, 1H), 3.11 (m, 1H), 3.03 (m, 1H), 2.92-2.83 (m, 2H), 2.68 (s, 3H), 2.64 (m, 2H), 2.58 (m, 1H), 2.46 (m, 1H), 2.33 (m, 1H), 2.27 (s, 6H), 1.92 (m, 1H), 1.76 (m, 4H), 1.67 (m, 1H), 1.57 (m, 1H), 1.48 (s, 3H), 1.38 (d, 3H), 1.31 (d, 3H), 1.33 (s, 3H), 1.25 (d, 3H), 1.15 (d, 3H), 1.09 (d, 3H), 0.87 (t, 3H).  
TLC: DCM/MeOH 10\1 (R<sub>f</sub>=0.25).

**Example 65****(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(4-(pyridin-3-yl)-imidazol-1-yl)-propylamino)-methylene]-erythromycin A**

A solution of example 6 (0.100g) and intermediate **52** (0.040g) in anhydrous DCM (4mL) was stirred at room temperature for 6h under nitrogen atmosphere. Then sodium cyanoborohydride (1M in THF, 0.150mL) and acetic acid (0.009mL) were added and the mixture stirred for 48h. The reaction was quenched with a saturated NaHCO<sub>3</sub> aqueous solution (10mL) and extracted with DCM (3x15mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was dissolved in MeOH (5mL) and heated to reflux temperature for 48h. After evaporating the solvent the crude material was purified by flash chromatography (eluting with: DCM/MeOH from 100\0 to 90\10) to give the title compound (0.008g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 9.00 (d, 1H), 8.45 (d, 1H), 8.11 (d, 1H), 7.59 (d, 1H), 7.39 (d, 1H), 7.29 (m, 1H), 5.55 (dd, 1H), 4.29 (d, 1H), 4.24 (d, 1H), 4.13 (s, 1H), 4.20-4.0 (m, 2H), 3.86 (q, 1H), 3.55 (m, 1H), 3.19 (m, 1H), 3.09 (m, 1H), 3.05 (m, 1H), 2.93 (m, 2H), 2.67 (s, 3H), 2.52 (m, 1H), 2.49 (m, 1H), 2.32 (d, 1H), 2.27 (s, 6H), 2.02 (m, 1H), 1.94 (m, 2H), 1.80 (m, 2H), 1.65 (m, 1H), 1.60 (m, 1H), 1.49 (s, 3H), 1.39 (d, 3H), 1.33 (s, 3H), 1.31 (d, 3H), 1.25 (m, 1H), 1.24 (d, 3H), 1.16 (d, 3H), 1.09 (d, 3H), 0.87 (t, 3H).

**Example 66****(11S,21S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(4-(pyridin-3-yl)-imidazol-1-yl)-propylamino)-methylene]-erythromycin A**

A solution of example 7 (0.500g) and intermediate **52** (0.180g) in anhydrous acetonitrile (7mL) was stirred at room temperature for 2h under nitrogen atmosphere. The solvent was evaporated and the residue dissolved in anhydrous MeOH (5mL). Then sodium cyanoborohydride (1M in THF, 0.375ml) and acetic acid (0.045ml) were added under nitrogen atmosphere and the mixture stirred overnight. The reaction was quenched with a saturated NaHCO<sub>3</sub> aqueous solution (10mL) and extracted with DCM (3x15mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM /MeOH 90\10) to give the title compound (0.170g, (21S) isomer 95% pure by NMR analysis).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 9.00 (d, 1H), 8.45 (d, 1H), 8.11 (d, 1H), 7.59 (d, 1H), 7.39 (d, 1H), 7.29 (m, 1H), 5.55 (dd, 1H), 4.29 (d, 1H), 4.24 (d, 1H), 4.13 (s, 1H), 4.20-4.0 (m, 2H), 3.86 (q, 1H), 3.55 (m, 1H), 3.19 (m, 1H), 3.09 (m, 1H), 3.05 (m, 1H), 2.93 (m, 2H), 2.67 (s, 3H), 2.52 (m, 1H), 2.49 (m, 1H), 2.32 (d, 1H), 2.27 (s, 6H), 2.02 (m, 1H), 1.94 (m, 2H), 1.80 (m, 2H),

1.65 (m, 1H), 1.60 (m, 1H), 1.49 (s, 3H), 1.39 (d, 3H), 1.33 (s, 3H), 1.31 (d, 3H), 1.25 (m, 1H), 1.24 (d, 3H), 1.16 (d, 3H), 1.09 (d, 3H), 0.87 (t, 3H).

#### Example 67

5 **(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(4-(pyridin-3-yl)-imidazol-1-yl)-butylamino)-methylene]-erythromycin A**

A solution of example 6 (0.100g) and intermediate 54 (0.050g) in anhydrous DCM (3mL) was stirred at room temperature for 24h under nitrogen atmosphere. Then sodium cyanoborohydride (1M in THF, 0.120mL) and acetic acid (0.008mL) were added under  
10 nitrogen atmosphere and the mixture stirred for 1h. The reaction was quenched with a saturated NaHCO<sub>3</sub> aqueous solution (5mL) and extracted with DCM (3x10mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH from 95\5 to 90\10) to give a compound that was dissolved in MeOH (2mL) and stirred at room temperature overnight.

15 Solvent evaporation under reduced pressure gave the title compound (0.015g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.98 (d, 1H), 8.46 (d, 1H), 8.09 (d, 1H), 7.56 (d, 1H), 7.36 (d, 1H), 7.30 (m, 1H), 5.67 (dd, 1H), 4.30 (d, 1H), 4.24 (d, 1H), 4.13 (s, 1H), 4.00 (m, 2H), 3.85 (q, 1H), 3.56 (m, 1H), 3.19 (m, 1H), 3.09 (m, 1H), 3.03 (m, 1H), 2.91 (m, 2H), 2.64 (s, 3H), 2.58 (m, 1H), 2.47 (m, 1H), 2.28 (m+s, 6H +1H), 2.00 (m, 1H), 1.89 (m, 2H), 1.79 (m, 1H), 1.70 (m, 2H), 1.60-1.50 (m, 2H), 1.48 (s, 3H), 1.39 (d, 3H), 1.31 (s, 3H), 1.31 (d, 3H), 1.25 (d, 3H), 1.25 (m, 1H), 1.15 (d, 3H), 1.09 (d, 3H), 0.83 (t, 3H).

#### Example 68

25 **(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(5-(4-(pyridin-3-yl)-imidazol-1-yl)-pentylamino)-methylene]-erythromycin A**

A solution of example 6 (0.080g) and intermediate 56 (0.042g) in anhydrous DCM (5mL) was stirred at room temperature for 1h under nitrogen atmosphere. Then sodium cyanoborohydride (1M in THF, 0.120mL) and HCl (2N in Et<sub>2</sub>O, 0.010mL) were added under  
30 nitrogen atmosphere and the mixture stirred for 1h. The reaction was quenched with a saturated NaHCO<sub>3</sub> aqueous solution (10mL) and extracted with DCM (3x15mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with DCM/MeOH from 96\4 to 90\10) to give a compound that was dissolved in MeOH (3mL) and stirred at room temperature overnight. Solvent evaporation under reduced pressure gave the title compound (0.013g).

35 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.99 (d, 1H), 8.47 (d, 1H), 8.10 (d, 1H), 7.55 (s, 1H), 7.31 (s, 1H), 7.29 (m, 1H), 5.67 (dd, 1H), 4.30 (d, 1H), 4.25 (d, 1H), 4.11 (s, 1H), 3.96 (m, 2H), 3.85 (q, 1H), 3.58 (m, 1H), 3.18 (dd, 1H), 3.09 (m, 1H), 3.02 (m, 1H), 2.90-2.75 (m, 2H), 2.67 (s, 3H), 2.58 (m, 1H), 2.46 (m, 1H), 2.29 (d, 1H), 2.27 (s, 6H), 1.90-1.86 (m, 3H), 1.78 (m, 1H), 1.70 (m, 2H), 1.60-1.50 (m, 3H), 1.47 (s, 3H), 1.5-1.4 (m, 4H), 1.38 (d, 3H), 1.33 (s, 3H), 1.32 (d, 3H),  
40 1.28 (d, 3H), 1.25 (m, 1H), 1.15 (d, 3H), 1.09 (d, 3H), 0.85 (t, 3H).

#### Example 69

**(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(4-(pyridin-3-yl)-imidazol-1-yl)-ethylamino)-methylene]-erythromycin A**

A solution of intermediate **51** (0.040g) in acetonitrile (1mL) and a 2M HCl aqueous solution (3mL) was heated to 80°C for 3h. The reaction mixture was allowed to reach room temperature, then it was added dropwise to a solution of example **6** (0.100g) dissolved in anhydrous acetonitrile (4mL) keeping the pH of the solution in the range 6-7 by addition of a saturated NaHCO<sub>3</sub> aqueous solution. The solution was stirred at room temperature for 2h. Acetic acid was added to the mixture to reach pH 5-6 followed by sodium cyanoborohydride (1M in THF, 0.150mL). The reaction mixture was stirred overnight at room temperature. After evaporating the solvent a saturated NaHCO<sub>3</sub> aqueous solution (5mL) was added and the product was extracted with DCM (3x10mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The crude material was purified by flash chromatography (eluting with DCM/MeOH 94/6) affording the title compound (0.027g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 9.04 (d, 1H), 8.46 (dd, 1H), 8.12 (d, 1H), 7.61 (d, 1H), 7.56 (m, 1H), 7.30 (m, 1H), 5.63 (dd, 1H), 4.27 (d, 1H), 4.22 (d, 1H), 4.19 (d, 1H), 4.20-4.08 (m, 2H), 3.84 (q, 1H), 3.54 (m, 1H), 3.36-3.19 (m, 2H), 3.16 (dd, 1H), 3.05 (m, 2H), 2.55 (m, 1H), 2.44 (m, 1H), 2.43 (s, 3H), 2.28 (s, 1H), 2.27 (s, 6H), 1.85 (m, 1H), 1.75 (m, 1H), 1.70-1.65 (m, 2H), 1.55 (m, 1H), 1.48 (s, 3H), 1.40 (d, 3H), 1.30 (d, 3H), 1.24-1.20 (m, 4H), 1.23 (s, 3H), 1.14 (d, 3H), 1.09 (d, 3H), 0.82 (t, 3H).

**Example 70**

**(11*S*,21*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(4-(pyridin-3-yl)-imidazol-1-yl)-ethylamino)-methylene]-erythromycin A**

A solution of intermediate **51** (0.530g) in acetonitrile (30mL) and a 3M HCl aqueous solution (20mL) was heated to 80°C for 3h. The reaction mixture was allowed to reach room temperature, then it was added dropwise to a solution of example **7** (0.500g) dissolved in anhydrous acetonitrile (2mL) keeping the pH of the solution in the range 6-7 by addition of saturated NaHCO<sub>3</sub> aqueous solution. The solution was stirred at room temperature for 1h. Acetic acid was added to the mixture to reach pH 5-6 followed by sodium cyanoborohydride (1M in THF, 0.75mL). The reaction mixture was stirred overnight at room temperature. After evaporating the solvent a saturated NaHCO<sub>3</sub> aqueous solution (15mL) was added and the mixture was extracted with DCM (3x20mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was dissolved in MeOH (10mL) and stirred overnight. After evaporating the solvent the crude material was purified by flash chromatography (eluting with DCM/MeOH from 98/2 to 90/10) to give the title compound (0.350g, (21*S*) isomer 95% pure by NMR analysis).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 9.04 (d, 1H), 8.46 (dd, 1H), 8.12 (d, 1H), 7.61 (d, 1H), 7.56 (m, 1H), 7.30 (m, 1H), 5.63 (dd, 1H), 4.27 (d, 1H), 4.22 (d, 1H), 4.19 (d, 1H), 4.20-4.08 (m, 2H), 3.84 (q, 1H), 3.54 (m, 1H), 3.36-3.19 (m, 2H), 3.16 (dd, 1H), 3.05 (m, 2H), 2.55 (m, 1H), 2.44 (m, 1H), 2.43 (s, 3H), 2.28 (s, 1H), 2.27 (s, 6H), 1.85 (m, 1H), 1.75 (m, 1H), 1.70-1.65 (m, 2H), 1.55 (m, 1H), 1.48 (s, 3H), 1.40 (d, 3H), 1.30 (d, 3H), 1.24-1.20 (m, 4H), 1.23 (s, 3H), 1.14 (d, 3H), 1.09 (d, 3H), 0.82 (t, 3H).

**Example 71****(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(5-quinolin-4-yl)-pentylamino)-methylene]-erythromycin A**

5 A solution of example 6 (0.084g) and intermediate 63 (0.040g) in anhydrous DCM (4mL) was stirred at room temperature for 1h under nitrogen atmosphere. Then sodium cyanoborohydride (1M in THF, 0.125mL) and acetic acid (0.007mL) were added and the mixture stirred overnight. The reaction was quenched with a saturated NaHCO<sub>3</sub> aqueous solution (10mL) and extracted with DCM (3x10mL). The organic layer was dried over  
10 Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with DCM/MeOH 90/10) to give a compound that was dissolved in MeOH (3mL) and stirred at room temperature overnight. Solvent evaporation under reduced pressure gave the title compound (0.006g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.81 (d, 1H), 8.11 (d, 1H), 8.06 (d, 1H), 7.70 (t, 1H), 7.57 (t, 1H), 7.26 (d, 1H), 5.71 (dd, 1H), 4.31 (d, 1H), 4.26 (d, 1H), 4.12 (d, 1H), 3.85 (q, 1H), 3.55 (m, 1H),  
15 3.19 (m, 1H), 3.10 (m, 1H), 3.07 (m, 2H), 3.03 (m, 1H), 2.90 (m, 1H), 2.80 (m, 1H), 2.68 (s, 3H), 2.58 (m, 1H), 2.45 (m, 1H), 2.30 (d, 1H), 2.27 (s, 6H), 1.90 (m, 1H), 1.75 (m, 2H), 1.70 (m, 3H), 1.52 (m, 2H), 1.48 (s, 3H), 1.37 (d, 3H), 1.33 (s, 3H), 1.32 (d, 3H), 1.24 (m, 1H), 1.25 (d, 3H), 1.15 (d, 3H), 1.09 (d, 3H), 0.85 (t, 3H).

**Example 72****(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-quinolin-4-yl)-propylamino)-methylene]-erythromycin A**

A solution of example 6 (0.100g) and 3-quinolin-4-yl-propionaldehyde (0.031g) in anhydrous  
25 DCM (4mL) was stirred at room temperature for 2h under nitrogen atmosphere. Then sodium cyanoborohydride (1M in THF, 0.150mL) and acetic acid (0.009mL) were added and the mixture stirred overnight. The reaction was quenched with a saturated NaHCO<sub>3</sub> aqueous solution (10mL) and extracted with DCM (3x10mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash  
30 chromatography (eluting with DCM/MeOH 95/5) to give a compound that was dissolved in MeOH (3mL) and stirred at room temperature overnight. Solvent evaporation under reduced pressure gave the title compound (0.011g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.80 (d, 1H), 8.13-8.09 (d, 2H), 7.70 (t, 1H), 7.58 (t, 1H), 7.30 (m, 1H), 5.80 (dd, 1H), 4.31 (d, 1H), 4.26 (d, 1H), 4.19 (s, 1H), 3.86 (q, 1H), 3.56 (m, 1H), 3.50 (bm, 1H), 3.26 (m, 1H), 3.19 (m, 1H), 3.12 (m, 1H), 3.06 (m, 3H), 2.90 (m, 1H), 2.69 (s, 3H), 2.58 (m, 1H), 2.46 (m, 1H), 2.36 (d, 1H), 2.27 (s, 6H), 1.92 (m, 3H), 1.80-1.70 (m, 2H), 1.65 (m, 1H), 1.60 (m, 1H), 1.50 (s, 3H), 1.40 (d, 3H), 1.33 (s+d, 3H+3H), 1.24 (m, 4H), 1.16 (d, 3H), 1.11 (d, 3H), 0.87 (t, 3H).

**Example 73****(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-quinolin-4-yl)-butylamino)-methylene]-erythromycin A**

A solution of example 6 (0.130g) and intermediate 59 (0.047g) in anhydrous THF (5mL) was stirred at room temperature for 1hr under nitrogen atmosphere. Then sodium cyanoborohydride (1M in THF, 0.195mL) and acetic acid until pH=5 were added and the mixture stirred for 3h. The reaction was quenched with a saturated NaHCO<sub>3</sub> aqueous solution (10mL) and extracted with DCM (3x10mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with DCM/MeOH from 98/2 to 96/4) to give a compound that was dissolved in MeOH (5mL) and stirred at room temperature overnight. Solvent evaporation under reduced pressure gave the title compound (0.015g).

m/z ([MH]<sup>+</sup>) = 810.

#### Example 74

##### (11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-quinolin-4-yl)-ethylamino)-methylene]-erythromycin A

A solution of intermediate 57 (0.270g) in acetonitrile (4mL) and 3M HCl aqueous solution (4mL) was heated to 50°C for 24h. The reaction mixture was allowed to reach room temperature, then it was added dropwise to a solution of example 6 (0.500g) in anhydrous acetonitrile (4mL) keeping the pH of the solution in the range 6-7 by addition of a saturated NaHCO<sub>3</sub> aqueous solution. The solution was stirred at room temperature for 3h. Acetic acid was added to the mixture to reach pH 5-6 followed by sodium cyanoborohydride (1M in THF, 0.75mL). The reaction mixture was stirred overnight at room temperature. After evaporating the solvent a saturated NaHCO<sub>3</sub> aqueous solution (15mL) was added and the mixture was extracted with DCM (3x20mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The residue was dissolved in MeOH (10mL) and stirred overnight. After solvent evaporation the crude material was purified by flash chromatography (eluting with DCM/MeOH from 98/2 to 90/10) to give the title compound (0.190g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.79 (d, 1H), 8.09 (m, 1H), 7.69 (t, 1H), 7.56 (t, 1H), 7.38 (d, 1H), 5.68 (dd, 1H), 4.29 (d, 1H), 4.22 (d, 1H), 4.21 (s, 1H), 3.83 (q, 1H), 3.54 (m, 1H), 3.41-3.1 (m, 4H), 3.17 (dd, 1H), 3.07 (m, 1H), 3.02 (m, 1H), 2.45 (m, 2H + -OCH<sub>3</sub>), 2.30 (m, 1H), 2.27 (s, N(CH<sub>3</sub>)<sub>2</sub>), 1.88 (m, 1H), 1.75 (m, 2H), 1.66 (m, 1H), 1.55 (m, 1H), 1.47 (s, 3H), 1.37 (d, 3H), 1.30 (d, 3H), 1.25 (d, 3H), 1.25 (m, 4H), 1.12 (d, 3H), 1.08 (d, 3H), 0.85 (t, 3H).

#### Example 75

##### (11S,21S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-quinolin-4-yl)-ethylamino)-methylene]-erythromycin A

A solution of intermediate 57 (0.832g) in acetonitrile (16mL) and a 3M HCl aqueous solution (16mL) was heated to 50°C for 16h. The reaction mixture was allowed to reach room temperature, then it was added dropwise to a solution of example 7 (1.500g) in anhydrous acetonitrile (12mL) keeping the pH of the solution in the range 6-7 by addition of a saturated NaHCO<sub>3</sub> aqueous solution. The solution was stirred at room temperature for 1h. Acetic acid was added to the mixture to reach pH 5-6 followed by sodium cyanoborohydride (1M in THF, 3.3mL). The reaction mixture was stirred overnight at room temperature. After evaporating

the solvent water (100mL) was added and the mixture extracted with EtOAc (2x100mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The crude material was purified by flash chromatography (DCM\MeOH 95\5). The obtained compound was dissolved in MeOH (20mL) and stirred overnight. After solvent evaporation the compound was purified by flash chromatography (eluting with DCM\MeOH 95\5) to give the title compound (0.365g, (21*S*) isomer 95% pure by NMR analysis).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.79 (d, 1H), 8.09 (m, 1H), 7.69 (t, 1H), 7.56 (t, 1H), 7.38 (d, 1H), 5.68 (dd, 1H), 4.29 (d, 1H), 4.22 (d, 1H), 4.21 (s, 1H), 3.83 (q, 1H), 3.54 (m, 1H), 3.41-3.1 (m, 4H), 3.17 (dd, 1H), 3.07 (m, 1H), 3.02 (m, 1H), 2.45 (m, 2H + 3H), 2.30 (m, 1H), 2.27 (s, 6H), 1.88 (m, 1H), 1.75 (m, 2H), 1.66 (m, 1H), 1.55 (m, 1H), 1.47 (s, 3H), 1.37 (d, 3H), 1.30 (d, 3H), 1.25 (d, 3H), 1.25 (m, 4H), 1.12 (d, 3H), 1.08 (d, 3H), 0.85 (t, 3H).

#### **Example 76**

##### **(11*S*,21*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((quinolin-4-yl)-methylamino)-methylene]-erythromycin A**

A solution of example 7 (0.050g) and quinoline-4-carbaldehyde (0.020g) in anhydrous toluene (3mL) was stirred at 100°C for 16h under nitrogen atmosphere. After evaporation of the solvent the crude material was dissolved in anhydrous MeOH (5mL) palladium (10wt. % on carbon powder, 0.006g) was added and the mixture stirred under hydrogen atmosphere (1 atm) for 5h. Filtration through a celite pad eluting with MeOH and purification by flash chromatography (eluting with: DCM\MeOH 93\7) gave the title compound (0.007g).

m/z ([MH]<sup>+</sup>) = 768

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.89 (d, 1H), 8.11 (d, 1H), 8.09 (d, 1H), 7.69 (t, 1H), 7.60 (t, 1H), 7.56 (t, 1H), 4.65 (m, 1H), 4.48 (m, 1H), 4.38 (m, 1H), 3.09 (m, 1H), 2.43 (m, 1H), 1.14 (d, 3H).

#### **Example 77**

##### **(11*S*,21*R,S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(5-methyl-furan-2-yl)-butylamino)-methylene]-erythromycin A**

A solution of 3-(5-methyl-2-furyl)butanal (0.030g) and example 6 (0.067g) in anhydrous acetonitrile (1mL) was stirred at room temperature for 5h under nitrogen atmosphere. Then sodium cyanoborohydride (1M in THF, 0.250mL) and acetic acid (0.025mL) were added and the mixture was stirred at room temperature for 24h. MeOH (1mL) was added and the reaction mixture heated to 60°C for 24h. After evaporation under reduced pressure the residue was dissolved in DCM (10mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The crude material was purified by flash chromatography (eluting with: DCM\MeOH\NH<sub>4</sub>OH 95\5\0.5) to give the title compound (0.029g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 5.82 (m, 2H), 4.10 (m, 1H), 3.02 (m, 1H), 2.86 (s, 2H), 2.77 (m, 1H), 2.40-2.20 (m, 3H+1H), 1.80-1.60 (m, 2H), 1.08 (d, 3H).

#### **Example 78**

**(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-pyridin-4-yl-prop-2-enylamino)-methylene]-erythromycin A**

A solution of 3-(5-methyl-2-furyl)butanal oxalate (0.045g), example 6 (0.067g) and DIPEA (0.051mL) in anhydrous acetonitrile (1mL) was stirred at room temperature for 1.5h under nitrogen atmosphere. Then sodium cyanoborohydride (1M in THF, 0.250mL) and acetic acid (0.025mL) were added and the mixture was stirred at room temperature for 15h. MeOH (1mL) was added and the reaction mixture heated to 60°C for 48h. After evaporation under reduced pressure the residue was dissolved in DCM (10mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM, DCM/MeOH/NH<sub>4</sub>OH from 96/4/0.1 to 92/8/0.2) to give the title compound (0.016g).

$m/z$  ( $[MH]^+$ ) = 744.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.52 (d, 2H), 7.28 (d, 2H), 6.59 (dd, 2H), 4.24 (m, 1H), 3.65 (m, 2H), 3.05 (m, 1H), 2.38 (m, 1H), 1.10 (d, 3H).

**Example 79**

**(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(4-(3,5-difluoro-phenyl)-pyrazol-1-yl)-propylamino)-methylene]-erythromycin A**

To a solution of example 7 (0.030g) in anhydrous THF (1mL) intermediate 75 (0.050g) was added and the mixture was stirred at room temperature for 3h under nitrogen atmosphere. Then sodium cyanoborohydride (1M in THF, 0.150mL) and acetic acid (0.010mL) were added and the mixture was allowed to react for 4h. The solvent was evaporated under reduced pressure, the residue dissolved in DCM (5mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was dissolved in MeOH (1mL) and the mixture stirred overnight. After evaporation of the solvent the crude material was purified by flash chromatography (eluting with: DCM/MeOH 90/10) to give the title compound ((0.014g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.83 (s, 1H), 7.73 (s, 1H), 7.03 (dd, 1H), 6.62 (tt, 1H), 4.28 (m, 2H), 4.12 (s, 1H), 3.04 (m, 1H), 2.91 (m, 1H), 2.82 (m, 1H), 2.32 (bs, 2H), 2.07 (m, 1H), 2.00 (m, 1H), 1.09 (d, 3H).

**Example 80**

**(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(4-(4-chloro-phenyl)-2,5-dimethyl-imidazol-1-yl)-propylamino)-methylene]-erythromycin A**

A solution of example 7 (0.050g) and intermediate 76 (0.025g) in anhydrous acetonitrile (1.5mL) was stirred at room temperature for 5h under nitrogen atmosphere. The solvent was evaporated under reduced pressure, the residue dissolved in anhydrous MeOH (1.5mL) then sodium cyanoborohydride (1M in THF, 0.037mL) and acetic acid (0.005mL) were added. After 18h the solvent was evaporated under reduced pressure, the residue dissolved in DCM (5mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x3mL). The organic phase



was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH 95/5) to give the title compound (0.028g).

5 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.55 (d, 2H), 7.33 (d, 2H), 4.15 (m, 1H), 4.00 (m, 1H), 3.85 (m, 1H), 3.05 (m, 1H), 3.02-2.90 (m, 2H), 2.42 (s, 3H), 2.35 (s, 3H), 2.33 (m, 1H), 1.90 (m, 1H), 1.72 (m, 1H), 1.09 (d, 3H).

#### Example 81

##### (11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(4-nitro-phenyl)-imidazol-1-yl)-propylamino)-methylene]-erythromycin A

10 A solution of example 7 (0.050g) and intermediate 77 (0.023g) in anhydrous acetonitrile (1.5mL) was stirred at room temperature for 18h under nitrogen atmosphere. The solvent was evaporated under reduced pressure, the crude dissolved in anhydrous MeOH (2mL) then sodium cyanoborohydride (1M in THF, 0.037mL) and acetic acid (0.005mL) were added.  
15 After 24h the solvent was evaporated under reduced pressure, the residue dissolved in DCM (5mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH 95/5) to give the title compound (0.007g).

20 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.24 (d, 2H), 7.96 (d, 2H), 7.61 (d, 1H), 7.54 (d, 1H), 4.14 (m, 1H), 4.20÷4.06 (m, 2H), 3.00÷2.88 (m, 2H), 2.32 (m, 1H), 2.03 (m, 1H), 1.92 (m, 1H).

#### Example 82

##### (11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(4-pyridin-4-yl-imidazol-1-yl)-propylamino)-methylene]-erythromycin A

25 A solution of example 7 (0.050g) and intermediate 78 (0.025g) in anhydrous acetonitrile (2mL) was stirred at room temperature for 16h under nitrogen atmosphere then heated to 50°C for 4h. After evaporating the solvent under reduced pressure, the crude was dissolved in anhydrous MeOH (2mL) then sodium cyanoborohydride (1M in THF, 0.100mL) and acetic acid (0.006mL) were added. After 24h the solvent was removed under reduced pressure, the residue dissolved in DCM (5mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH 90/10) to give the title compound (0.014g).

35 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.57 (d, 1H), 7.70 (d, 1H), 7.62 (s, 1H), 7.52 (s, 1H), 4.20-4.16 (m, 2H), 3.05 (m, 1H), 2.96-2.88 (m, 2H), 2.32 (m, 1H), 2.02 – 1.92 (m+m, 2H), 1.10 (d, 3H).

#### Example 83

##### (11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(3-trifluoromethyl-1H-pyrazol-4-yl)-propylamino)-methylene]-erythromycin A

40 A solution of example 7 (0.020g) and intermediate 79 (0.015g) in anhydrous acetonitrile (2mL) was stirred at room temperature for 3h under nitrogen atmosphere then heated to 40°C

for 4h. After evaporating the solvent under reduced pressure, the crude material was dissolved in anhydrous MeOH (2mL) then sodium cyanoborohydride (1M in THF, 0.015mL) and acetic acid (0.003mL) were added. After 24h the solvent was removed under reduced pressure, the residue dissolved in DCM (5mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH from 100/0 to 98/2) to give the title compound (0.004g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.53 (s, 1H), 4.12 (d, 1H), 3.03 (m, 1H), 2.92 (m, 1H), 2.84 (m, 1H), 2.70-2.60 (m, 2H), 2.11 (m, 1H), 1.70 (m, 2H), 1.09 (d, 3H).

#### **Example 84**

##### **(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(5-methyl-4-(4-trifluoromethyl-phenyl)-imidazol-1-yl)-propylamino)-methylene]-erythromycin A**

A solution of example 7 (0.050g) and intermediate 80 (0.038g) in anhydrous acetonitrile (1mL) was stirred at room temperature overnight under nitrogen atmosphere. The solvent was evaporated under reduced pressure, the crude dissolved in anhydrous MeOH (1mL) then sodium cyanoborohydride (1M in THF, 0.037mL) and acetic acid (0.004mL) were added. After 24h the solvent was removed under reduced pressure, the residue dissolved in DCM (5mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH/NH<sub>4</sub>OH from 98/2/0 to 95/5/0.5) and by preparative TLC (DCM/MeOH/NH<sub>4</sub>OH 90/9/0.5) to give the title compound (0.017g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.78 (d, 2H), 7.64 (d, 2H), 7.59 (s, 1H), 5.60 (dd, 1H), 4.30 (d, 1H), 4.25 (d, 1H), 4.15 (s, 1H), 4.10 (m, 1H), 3.96 (m, 1H), 3.86 (q, 1H), 3.56 (m, 1H), 3.19 (dd, 1H), 3.09 (m, 1H), 3.04 (m, 1H), 2.96 (m, 2H), 2.68 (s, 3H), 2.58 (m, 1H), 2.45 (m, 1H), 2.42 (s, 3H), 2.33 (s, 1H), 2.27 (s, 6H), 2.00÷1.88 (2H), 1.90 (m, 1H), 1.81 (dd, 1H), 1.73 (bd, 1H), 1.67 (m, 1H), 1.60 (m, 1H), 1.49 (s, 3H), 1.38 (d, 3H), 1.34 (s, 3H), 1.32 (d, 3H), 1.25 (m, 1H), 1.25 (d, 3H), 1.16 (d, 3H), 1.10 (d, 3H), 0.88 (t, 3H).

#### **Example 85**

##### **(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(pyridin-3-yl)-propylamino)-methylene]-erythromycin A**

A solution of example 7 (0.050g) and intermediate 81 (0.020g) in anhydrous acetonitrile (0.7mL) was stirred at room temperature for 3h under nitrogen atmosphere. The solvent was evaporated under reduced pressure, the crude dissolved in anhydrous MeOH (1mL) then sodium cyanoborohydride (1M in THF, 0.035mL) and acetic acid (0.004mL) were added. After 18h the solvent was removed under reduced pressure, the residue dissolved in DCM (5mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was

purified by flash chromatography (eluting with: DCM/MeOH 95/5) to give the title compound (0.009g).

$m/z$  ( $[MH]^+$ ) = 746.

$^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 8.47-8.40 (m, 2H), 7.51 (m, 1H), 7.19 (m, 1H), 4.14 (m, 1H), 3.03 (m, 1H), 2.98-2.85 (m, 2H), 2.75-2.60 (m, 2H), 2.31 (bm, 1H), 1.82-1.76 (m, 2H), 1.09 (d, 3H).

#### **Example 86**

##### **(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(4-pyridin-2-yl-pyrazol-1-yl)-propylamino)-methylene]-erythromycin A**

A solution of example 7 (0.050g) and intermediate **82** (0.025g) in anhydrous acetonitrile (3mL) was stirred at 50°C for 3h and at room temperature overnight under nitrogen atmosphere. The solvent was evaporated under reduced pressure, the crude dissolved in anhydrous MeOH (2.2mL) then sodium cyanoborohydride (1M in THF, 0.040mL) and acetic acid (0.020mL) were added. After 10h the solvent was removed under reduced pressure, the residue dissolved in DCM (5mL) and washed with a saturated  $NaHCO_3$  aqueous solution (2x3mL). The organic phase was dried over  $Na_2SO_4$  and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH 95/5) to give the title compound (0.026g).

$^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 8.54 (d, 1H), 8.01 (s, 1H), 7.98 (s, 1H), 7.65 (t, 1H), 7.50 (t, 1H), 7.07 (m, 1H), 4.27 (d, 1H), 4.14 (m, 2H), 3.04 (m, 1H), 2.89 (m, 2H), 2.34 (m, 1H), 2.12 (m, 1H), 2.03 (m, 1H), 1.09 (d, 3H).

#### **Example 87**

##### **(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(pyridin-4-yl)-propylamino)-methylene]-erythromycin A**

A solution of example 7 (0.050g) and intermediate **83** (0.050g) in anhydrous acetonitrile (1mL) was stirred at room temperature overnight under nitrogen atmosphere. The solvent was evaporated under reduced pressure, the crude dissolved in anhydrous MeOH (1mL) then sodium cyanoborohydride (1M in THF, 0.037mL) and acetic acid (0.004mL) were added. After 24h the solvent was removed under reduced pressure, the residue dissolved in DCM (5mL) and washed with a saturated  $NaHCO_3$  aqueous solution (2x3mL). The organic phase was dried over  $Na_2SO_4$  and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH from 100/0 to 90/10) and by preparative TLC (eluting with: DCM/MeOH/ $NH_4OH$  90/9/0.5) to give the title compound (0.014g).

$^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 8.47 (d, 2H), 7.13 (d, 2H), 5.70 (dd, 1H), 4.31 (d, 1H), 4.25 (d, 1H), 4.14 (s, 1H), 3.85 (q, 1H), 3.56 (m, 1H), 3.18 (dd, 1H), 3.10 (m, 1H), 3.03 (q, 1H), 2.95÷2.83 (m, 2H), 2.65÷2.55 (m, 2H), 2.67 (s, 3H), 2.59 (m, 1H), 2.46 (m, 1H), 2.31(s, 1H), 2.27 (s, 6H), 1.91 (m, 1H), 1.82÷1.76 (m, 3H), 1.73 (m, 1H), 1.68 (m, 1H), 1.58 (m, 1H), 1.48 (s, 3H), 1.39 (d, 3H), 1.34 (s, 3H), 1.32 (d, 3H), 1.25 (m, 1H), 1.25 (d, 3H), 1.15 (d, 3H), 1.09 (d, 3H), 0.87 (t, 3H).

**Example 88****(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(4-pyrimidin-4-yl-pyrazol-1-yl)-propylamino)-methylene]-erythromycin A**

5 A solution of example 7 (0.028g) and intermediate 84 (0.018g) in anhydrous acetonitrile (1.5mL) was stirred at room temperature for 30min then heated to 50°C for 6h under nitrogen atmosphere. The solvent was evaporated under reduced pressure, the crude dissolved in anhydrous MeOH (2mL) then sodium cyanoborohydride (1M in THF, 0.025mL) and acetic acid (0.004mL) were added. After 24h the solvent was removed under reduced pressure, the residue dissolved in DCM (5mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution  
10 (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH from 100/0 to 97/3) to give the title compound (0.005g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 9.09 (d, 1H), 8.63 (d, 1H), 8.18 (s, 1H), 8.07 (s, 1H), 7.47 (d, 1H), 4.30 (m, 2H), 4.13 (s, 1H), 3.04 (m, 1H), 2.92-2.80 (m, 2H), 2.33 (m, 1H), 2.11 (m, 1H), 2.00 (m,  
15 1H), 1.09 (d, 3H).

**Example 89****(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(4-pyridin-4-yl-pyrazol-1-yl)-propylamino)-methylene]-erythromycin A**

20 A solution of example 7 (0.050g) and intermediate 85 (0.018g) in anhydrous acetonitrile (2.2mL) was stirred at 50°C for 16h under nitrogen atmosphere. The solvent was evaporated under reduced pressure, the crude dissolved in anhydrous MeOH (3mL) then sodium cyanoborohydride (1M in THF, 0.040mL) and acetic acid (0.020mL) were added. After 18h the solvent was removed under reduced pressure, the residue dissolved in DCM (5mL) and  
25 washed with a NaHCO<sub>3</sub> saturated aqueous solution (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH 95/5) to give the title compound (0.014g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.55 (d, 1H), 7.96 (s, 1H), 7.85 (s, 1H), 7.42 (d, 1H), 4.13 (d, 1H), 3.04 (m, 1H), 2.89 (m, 1H), 2.84 (m, 1H), 2.33 (m, 1H), 2.10 (m, 1H), 1.95 (m, 1H), 1.10 (d, 3H).  
30

**Example 90****(11S,21S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(4-(3,5-dichloro-phenyl)-2,5-dimethyl-imidazol-1-yl)-propylamino)-methylene]-erythromycin A**

35 A solution of example 7 (0.030g) and intermediate 86 (0.029g) in anhydrous acetonitrile (1.5mL) was stirred at room temperature for 5h under nitrogen atmosphere. The solvent was evaporated under reduced pressure, the crude dissolved in anhydrous MeOH (1.5mL) then sodium cyanoborohydride (1M in THF, 0.022mL) and acetic acid (0.003mL) were added. After 12h the solvent was removed under reduced pressure, the residue dissolved in DCM  
40 (5mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was

purified by flash chromatography (eluting with: DCM\MeOH from 100\0 to 97\3) to give the title compound (0.022g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.47 (d, 2H), 7.15 (t, 1H), 4.11 (m, 1H), 3.98 (m, 1H), 3.82 (m, 1H), 2.93 (m, 2H), 2.38 (s, 3H), 2.33 (s, 3H), 2.29 (m, 1H), 1.6÷1.8 (m, 2H).

5

#### Example 91

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(2,5-dimethyl-4-(3-trifluoromethyl-phenyl)-imidazol-1-yl)-propylamino)-methylene]-erythromycin A

10 A solution of example 7 (0.040g) and intermediate 87 (0.042g) in anhydrous acetonitrile (1.5mL) was stirred at room temperature for 4h under nitrogen atmosphere. The solvent was evaporated under reduced pressure, the crude dissolved in anhydrous MeOH (1.5mL) then sodium cyanoborohydride (1M in THF, 0.030mL) and acetic acid (0.004mL) were added. After 12h the solvent was removed under reduced pressure, the residue dissolved in DCM  
15 (5mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM\MeOH from 100\0 to 97\3) to give the title compound (0.026g).

20 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.84 (bs, 1H), 7.74 (m, 1H), 7.43 (m, 2H), 4.12 (s, 1H), 3.99 (m, 1H), 3.82 (m, 1H), 2.9÷2.88 (m, 2H), 2.40 (s, 3H), 2.33 (s, 3H), 2.30 (s, 1H), 1.85÷1.75 (m, 2H).

#### Example 92

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-[4-(1,3-benzoxazol-2-yl)-1H-pyrazol-1-yl]-propylamino)-methylene]-erythromycin A

25 A solution of example 7 (0.037g) and intermediate 88 (0.022g) in anhydrous acetonitrile (1.5mL) was stirred at 50°C for 6h under nitrogen atmosphere. The solvent was evaporated under reduced pressure, the crude dissolved in anhydrous MeOH (2mL) then sodium cyanoborohydride (1M in THF, 0.030mL) and acetic acid (0.004mL) were added. After 18h the solvent was removed under reduced pressure, the residue dissolved in DCM (5mL) and  
30 washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM\MeOH from 100\0 to 97\3) to give the title compound (0.007g).

35 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.17 (s, 1H), 8.14 (s, 1H), 7.68 (dd, 1H), 7.51 (dd, 1H), 7.29 (m, 2H), 4.34-4.29 (m, 2H), 4.14 (s, 1H), 3.03 (m, 1H), 2.90 (m, 2H), 2.33 (bm, 1H), 2.15 (m, 1H), 2.00 (m, 1H), 1.09 (d, 3H)

#### Example 93

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(5-Pyridin-4-yl-pyrazol-1-yl)-propylamino)-methylene]-erythromycin A

40 A solution of example 7 (0.050g) and intermediate 89 (0.036g) in anhydrous acetonitrile (1.5mL) was stirred at room temperature for 20h under nitrogen atmosphere. The solvent was

evaporated under reduced pressure, the crude dissolved in anhydrous MeOH (2mL) then sodium cyanoborohydride (1M in THF, 0.075mL) and acetic acid (0.010mL) were added. After 20h the solvent was removed under reduced pressure, the residue dissolved in DCM (5mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM\MeOH from 100\0 to 97\3) to give the title compound (0.011g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.60 (d, 1H), 7.69 (d, 1H), 7.52 (d, 1H), 6.62 (d, 1H), 4.29 (m, 2H), 4.14 (m, 1H), 3.04 (m, 1H), 2.88 (m, 2H), 2.33 (m, 1H), 2.20 (m, 1H), 1.98 (m, 1H), 1.10 (d, 3H).

#### **Example 94**

##### **(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(2-pyridin-4-yl-1H-imidazol-1-yl)-propylamino)-methylene]-erythromycin A**

A solution of example 7 (0.050g) and intermediate 90 (0.025g) in anhydrous acetonitrile (2mL) was stirred at 50°C for 6h then at room temperature overnight under nitrogen atmosphere. The solvent was evaporated under reduced pressure, the crude dissolved in anhydrous MeOH (2mL) then sodium cyanoborohydride (1M in THF, 0.150mL) and acetic acid (0.006mL) were added. After 72h the solvent was removed under reduced pressure, the residue dissolved in DCM (5mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM\MeOH 90\10) to give the title compound (0.014g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.27 (d, 1H), 7.59 (d, 1H), 7.19 (m, 1H), 7.16 (m, 1H), 4.30-4.10 (m, 3H), 3.15 (m, 2H), 2.96 (m, 1H), 2.31 (m, 1H), 2.00 – 1.82 (m, 2H), 1.09 (d, 3H).

#### **Example 95**

##### **(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(4-quinolin-2-yl-1H-pyrazol-1-yl)-propylamino)-methylene]-erythromycin A**

A solution of example 7 (0.050g) and intermediate 91 (0.032g) in anhydrous acetonitrile (1mL) was stirred at room temperature for 18h under nitrogen atmosphere. The solvent was evaporated under reduced pressure, the crude dissolved in anhydrous MeOH (1mL) then sodium cyanoborohydride (1M in THF, 0.037mL) and acetic acid (0.004mL) were added. After 18h the solvent was removed under reduced pressure, the residue dissolved in DCM (5mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM\MeOH from 98\2 to 94\6) and by preparative TLC (DCM\MeOH\NH<sub>4</sub>OH 90\9\0.5) to give the title compound (0.018g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.20 (s, 1H), 8.14 (s, 1H), 8.12 (d, 1H), 8.04 (d, 1H), 7.76 (d, 1H), 7.67 (t, 1H), 7.66 (d, 1H), 7.45 (t, 1H), 5.68 (dd, 1H), 4.31 (m, 3H), 4.26 (d, 1H), 4.15 (s, 1H), 3.86 (q, 1H), 3.56 (m, 1H), 3.18 (dd, 1H), 3.11 (m, 1H), 3.05 (m, 1H), 2.95÷2.80 (m, 2H), 2.70 (s, 3H), 2.58 (m, 1H), 2.46 (m, 1H), 2.35 (s, 1H), 2.27 (s, 6H), 2.14 (m, 1H), 2.06 (m, 1H), 1.96 (m, 1H), 1.80 (m, 1H), 1.74 (m, 1H), 1.70 (m, 1H), 1.65 (m, 1H), 1.50 (s, 3H),

1.40 (d, 3H), 1.34 (s, 3H), 1.32 (d, 3H), 1.25 (m, 1H), 1.24 (d, 3H), 1.16 (d, 3H), 1.10 (d, 3H), 0.90 (t, 3H).

#### Example 96

5 (11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(4-quinolin-4-yl-1*H*-pyrazol-1-yl)-propylamino)-methylene]-erythromycin A

A solution of example 7 (0.050g) and intermediate 92 (0.034g) in anhydrous acetonitrile (1mL) was stirred at room temperature for 18h under nitrogen atmosphere. The solvent was evaporated under reduced pressure, the crude dissolved in anhydrous MeOH (1mL) then sodium cyanoborohydride (1M in THF, 0.037mL) and acetic acid (0.004mL) were added. After 18h the solvent was removed under reduced pressure, the residue dissolved in DCM (5mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH from 98/2 to 94/6) to give the title compound (0.020g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.89 (d, 1H), 8.25 (d, 1H), 8.14 (d, 1H), 7.87 (s, 1H), 7.84 (s, 1H), 7.73 (m, 1H), 7.59 (m, 1H), 7.42 (d, 1H), 5.63 (dd, 1H), 4.37 (m, 2H), 4.30 (d, 1H), 4.24 (d, 1H), 4.16 (s, 1H), 3.85 (q, 1H), 3.55 (m, 1H), 3.18 (dd, 1H), 3.10 (m, 1H), 3.04 (m, 1H), 2.94 (m, 2H), 2.70 (s, 3H), 2.58 (m, 1H), 2.45 (m, 1H), 2.34 (s, 1H), 2.27 (s, 6H), 2.19 (m, 1H), 2.05 (m, 1H), 1.88 (m, 1H), 1.80 (dd, 1H), 1.73 (m, 1H), 1.67 (m, 1H), 1.56 (m, 1H), 1.49 (s, 3H), 1.38 (d, 3H), 1.33 (s, 3H), 1.32 (d, 3H), 1.25 (m, 1H), 1.24 (d, 3H), 1.15(d, 3H), 1.10 (d, 3H), 0.83 (t, 3H).

#### Example 97

25 (11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(4-quinoxalin-2-yl-1*H*-pyrazol-1-yl)-propylamino)-methylene]-erythromycin A

A solution of example 7 (0.050g) and intermediate 93 (0.030g) in anhydrous acetonitrile (1mL) was stirred at room temperature for 18h under nitrogen atmosphere. The solvent was evaporated under reduced pressure, the crude dissolved in anhydrous MeOH (1mL) then sodium cyanoborohydride (1M in THF, 0.037mL) and acetic acid (0.004mL) were added. After 18h the solvent was removed under reduced pressure, the residue dissolved in DCM (5mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH from 98/2 to 94/6) and by preparative TLC (DCM/MeOH/NH<sub>4</sub>OH 90/9/0.5) to give the title compound (0.006g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 9.10 (s, 1H), 8.28 (s, 1H), 8.22 (s, 1H), 8.03 (m, 2H), 7.73 (t, 1H), 7.66 (t, 1H), 5.63 (dd, 1H), 4.35 (m, 2H), 4.30 (d, 1H), 4.26 (d, 1H), 4.15 (m, 1H), 3.87 (q, 1H), 3.55 (m, 1H), 3.17 (m, 1H), 3.11 (m, 1H), 3.05 (m, 1H), 3.00±2.80 (m, 2H), 2.71 (s, 3H), 2.60 (m, 1H), 2.46 (m, 1H), 2.35 (m, 1H), 2.27 (s, 6H), 2.15 (m, 1H), 2.06 (m, 1H), 1.96 (m, 1H), 1.80 (m, 1H), 1.74 (m, 1H), 1.68 (m, 1H), 1.60 (m, 1H), 1.50 (s, 3H), 1.40 (d, 3H), 1.34 (s, 3H), 1.32 (d, 3H), 1.30 (m, 1H), 1.24 (d, 3H), 1.16 (d, 3H), 1.10 (d, 3H), 0.90 (t, 3H).

**Example 98****(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-thien-3-ylpropylamino)-methylene]-erythromycin A**

A solution of example 7 (0.042g) and intermediate 94 (0.025g) in anhydrous acetonitrile (2mL) was stirred at 50°C for 6h under nitrogen atmosphere. The solvent was evaporated under reduced pressure, the crude dissolved in anhydrous MeOH (2mL) then sodium cyanoborohydride (1M in THF, 0.035mL) and acetic acid (0.004mL) were added. After 18h at room temperature the solvent was removed under reduced pressure, the residue dissolved in DCM (5mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH from 100\0 to 98\2) to give the title compound (0.012g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.21 (m, 1H), 6.94 (m, 2H), 4.13 (m, 1H), 3.03 (m, 1H), 2.91 (m, 1H), 2.83 (m, 1H), 2.80-2.60 (m, 2H), 2.31 (m, 1H), 1.80 (m, 2H), 1.09 (d, 3H).

**Example 99****(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-[5-(3-methyl-pyrazin-2-yl)-pyrazol-1-yl]-propylamino)-methylene]-erythromycin A**

A solution of example 7 (0.050g) and intermediate 95 (0.037g) in anhydrous acetonitrile (1mL) was stirred at room temperature for 18h under nitrogen atmosphere. The solvent was evaporated under reduced pressure, the crude dissolved in anhydrous MeOH (2mL) then sodium cyanoborohydride (1M in THF, 0.075mL) and acetic acid (0.009mL) were added. After 20h the solvent was removed under reduced pressure, the residue dissolved in DCM (5mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH from 100\0 to 94\6) to give the title compound (0.018g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.44 (d, 1H), 8.36 (d, 1H), 7.54 (d, 1H), 6.82 (d, 1H), 4.40-4.20 (m, 2H), 4.14 (m, 1H), 3.04 (m, 1H), 2.90 (s, 3H), 2.89 (m, 2H), 2.33 (m, 1H), 2.15 (m, 1H), 2.05 (m, 1H), 1.10 (d, 3H).

**Example 100****(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-[2-(methylthio)-1H-benzimidazol-1-yl]-propylamino)-methylene]-erythromycin A**

A solution of example 7 (0.050g) and intermediate 96 (0.037g) in anhydrous acetonitrile (1mL) was stirred at room temperature for 3h under nitrogen atmosphere. The solvent was evaporated under reduced pressure, the crude dissolved in anhydrous MeOH (2mL) then sodium cyanoborohydride (1M in THF, 0.075mL) and acetic acid (0.009mL) were added. After 20h the solvent was removed under reduced pressure, the residue dissolved in DCM (5mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was



purified by flash chromatography (eluting with: DCM\MeOH from 98\2) to give the title compound (0.020g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.66 (m, 1H), 7.40 (m, 1H), 7.35 (m, 1H), 7.20 (m, 1H), 4.15 (m, 1H), 4.25 (m, 1H), 4.13 (m, 1H), 3.05 (m, 1H), 2.95 (m, 2H), 2.79 (m, 2H), 2.36 (m, 1H), 2.00 (m, 1H), 1.86 (m, 1H), 1.10 (d, 3H).

#### **Example 101**

##### **(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-[3-(4-chlorophenyl)-1H-pyrazol-5-yl]-propylamino)-methylene]-erythromycin A**

A solution of example 7 (0.040g) and intermediate 97 (0.035g) in anhydrous acetonitrile (1.5mL) was stirred at room temperature for 12h then heated to 50°C for 6h under nitrogen atmosphere. The solvent was evaporated under reduced pressure, the crude dissolved in anhydrous MeOH (1.5mL) then sodium cyanoborohydride (1M in THF, 0.030mL) and acetic acid (0.004mL) were added. After 12h the solvent was removed under reduced pressure, the residue dissolved in DCM (5mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM\MeOH from 100\0 to 97\3) to give the title compound (0.017g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.73 (d, 2H), 7.35 (d, 2H), 6.35 (s, 1H), 4.15 (m, 1H), 2.93 (m, 2H), 2.82 (m, 1H), 2.34 (m, 1H), 1.88 (m, 1H).

#### **Example 102**

##### **(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-[6-(methylthio)-7H-purin-7-yl]-propylamino)-methylene]-erythromycin A**

A solution of example 7 (0.040g) and intermediate 98 (0.042g) in anhydrous acetonitrile (1.5mL) was stirred at room temperature for 3h then heated to 50°C for 3h under nitrogen atmosphere. The solvent was evaporated under reduced pressure, the crude dissolved in anhydrous MeOH (1.5mL) then sodium cyanoborohydride (1M in THF, 0.060mL) and acetic acid (0.008mL) were added. After 6h the solvent was removed under reduced pressure, the residue dissolved in DCM (5mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM\MeOH from 100\0 to 98\2) to give the title compound (0.005g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.85 (m, 1H), 8.25 (s, 1H), 4.63 (m, 1H), 4.45 (m, 1H), 4.15 (m, 1H), 2.97 (m, 2H), 2.76 (s, 3H), 2.33 (m, 1H), 2.0÷2.2 (m, 2H).

#### **Example 103**

##### **(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(6-methoxy-7H-purin-7-yl)-propylamino)-methylene]-erythromycin A**

A solution of example 7 (0.050g) and intermediate 99 (0.031g) in anhydrous acetonitrile (1.5mL) was stirred at room temperature overnight under nitrogen atmosphere. The solvent was evaporated under reduced pressure, the crude dissolved in anhydrous MeOH (1.5mL)

then sodium cyanoborohydride (1M in THF, 0.074mL) and acetic acid (0.010mL) were added. After 4h the solvent was removed under reduced pressure, the residue dissolved in DCM (5mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH from 100/0 to 97/3) to give the title compound (0.015g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.54 (s, 1H), 8.07 (s, 1H), 5.58 (dd, 1H), 4.37 (t, 2H), 4.31 (d, 1H), 4.25 (d, 1H), 4.19 (s, 3H), 4.13 (bs, 1H), 3.86 (q, 1H), 3.55 (m, 1H), 3.20 (m, 1H), 3.10 (m, 1H), 3.04 (m, 1H), 2.89 (bm, 2H), 2.70 (s, 3H), 2.59 (m, 1H), 2.48 (bm, 1H), 2.34 (s, 1H), 2.29 (s, 6H), 2.12 (m, 1H), 2.04 (m, 1H), 1.95 (m, 1H), 1.85-1.48 (m, 5H), 1.49 (s, 3H), 1.39 (d, 3H), 1.34 (s, 3H), 1.32 (d, 3H), 1.25 (d+m, 3H+1H), 1.16 (d, 3H), 1.10 (d, 3H), 0.89 (t, 3H).

#### **Example 104**

##### **(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-foxycarbonyl-(3-(6-methoxy-2-oxo-1,3-benzoxazol-3(2H)-yl)-propylamino)-methylene]-erythromycin A**

A solution of example 7 (0.043g) and intermediate 100 (0.025g) in anhydrous acetonitrile (2mL) was stirred at room temperature for 30min then heated to 50°C for 6h under nitrogen atmosphere. The solvent was evaporated under reduced pressure, the crude dissolved in anhydrous MeOH (2mL) then sodium cyanoborohydride (1M in THF, 0.030mL) and acetic acid (0.005mL) were added. After 18h the solvent was removed under reduced pressure, the residue dissolved in DCM (5mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH from 100/0 to 97/3) to give the title compound (0.007g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.05 (d, 1H), 6.82 (d, 1H), 6.47 (dd, 1H), 4.13 (s, 1H), 3.87 (m, 2H), 3.81 (s, 3H), 3.04 (m, 1H), 2.97-2.92 (m, 2H), 2.34 (m, 1H), 1.96 (m, 1H), 1.80 (m, 1H), 1.09 (d, 3H).

#### **Example 105**

##### **(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-foxycarbonyl-(3-(1H-pyrrolo[2,3-b]pyridin-1-yl)-propylamino)-methylene]-erythromycin A**

A solution of example 7 (0.050g) and intermediate 101 (0.042g) in anhydrous acetonitrile (1.5mL) was stirred at room temperature for 6h under nitrogen atmosphere. The solvent was evaporated under reduced pressure, the crude dissolved in anhydrous MeOH (1.5mL) then sodium cyanoborohydride (1M in THF, 0.037mL) and acetic acid (0.005mL) were added. After 8h the solvent was removed under reduced pressure, the residue dissolved in DCM (5mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH/NH<sub>4</sub>OH 95/5/0.5) to give the title compound (0.006g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.30 (dd, 1H), 7.87 (dd, 1H), 7.30 (d, 1H), 7.03 (dd, 1H), 6.43 (d, 1H), 5.71 (dd, 1H), 4.44÷4.36 (m, 2H), 4.32 (d, 1H), 4.25 (d, 1H), 4.13 (s, 1H), 3.85 (q, 1H), 3.55

(m, 1H), 3.22 (dd, 1H), 3.11 (m, 1H), 3.04 (m, 1H), 2.90÷2.78 (m, 2H), 2.70 (s, 3H), 2.62÷2.50 (m, 2H), 2.35 (s, 1H), 2.32 (s, 6H), 2.06 (m, 1H), 2.00 (m, 1H), 1.95 (m, 1H), 1.80÷1.68 (m, 3H), 1.58 (m, 1H), 1.49 (s, 3H), 1.39 (d, 3H), 1.33 (s, 3H), 1.32 (d, 3H), 1.25 (m, 1H), 1.25 (d, 3H), 1.15 (d, 3H), 1.10 (d, 3H), 0.89 (t, 3H).

5

**Example 106****(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-ethylamino)-methylenel]-erythromycin A**

To a solution of example 13 (0.232g) in anhydrous DMF (5mL) 2-[(1,3-thiazol-2-ylamino)carbonyl]benzoic acid (0.097g), (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (0.186g) and DIPEA (0.120mL) were added and the resulting mixture was stirred overnight at room temperature. It was diluted with DCM (10mL) and washed with a 5% NaHCO<sub>3</sub> aqueous solution (2x5mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was dissolved in DCM (5mL) loaded on SCX-cartridge (5g, loading 0.75mmol/g, previously washed with 50mL of MeOH), washed with MeOH (50mL), then the product eluted with NH<sub>3</sub> (0.25M solution in MeOH, 60mL), followed by MeOH (10mL). Solvent evaporation gave the title compound (0.170g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.80 (m, 2H), 7.67 (m, 2H), 5.53 (dd, 1H), 4.30 (d, 1H), 4.24 (d, 1H), 4.17 (s, 1H), 3.84 (m, 2H), 3.74 (m, 1H), 3.55 (m, 1H), 3.20-3.15 (m, 2H), 3.12-2.88 (m, 3H), 2.63 (s, 3H), 2.54 (m, 1H), 2.47 (m, 1H), 2.30 (m, 1H), 2.27 (s, 6H), 1.86 (m, 1H), 1.75-1.65 (m, 3H), 1.48 (m, 1H), 1.43 (s, 3H), 1.29 (s, 3H), 1.28-1.24 (m, 2\*3H+1H), 1.19 (d, 3H), 1.12 (d, 3H), 1.06 (d, 3H), 0.73 (t, 3H).

**Example 107****(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-[3-(2,4-dimethyl-1,3-thiazol-5-yl)-1H-pyrazol-1-yl]-propylamino)-methylenel]-erythromycin A**

A solution of example 7 (0.050g) and intermediate 102 (0.042g) in anhydrous acetonitrile (1mL) was stirred at room temperature for 6h under nitrogen atmosphere. The solvent was evaporated under reduced pressure, the crude dissolved in anhydrous MeOH (2mL) then sodium cyanoborohydride (1M in THF, 0.070mL) and acetic acid (0.009mL) were added. After 20h the solvent was removed under reduced pressure, the residue dissolved in DCM (5mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH from 98/2) to give the title compound (0.016g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.49 (d, 1H), 6.36 (d, 1H), 5.62 (dd, 1H), 4.31 (d, 1H), 4.25 (d, 1H), 4.23 (m, 2H), 4.13 (s, 1H), 3.85 (q, 1H), 3.56 (m, 1H), 3.19 (m, 1H), 3.10 (m, 1H), 3.03 (m, 1H), 2.92÷2.82 (m, 2H), 2.69 (s, 3H), 2.66 (s, 3H), 2.58 (m, 1H), 2.55 (s, 3H), 2.47 (m, 1H), 2.33 (s, 1H), 2.28 (s, 6H), 2.08 (m, 1H), 1.98 (m, 1H), 1.94 (m, 1H), 1.80 (m, 1H), 1.76÷1.66 (m, 2H), 1.62÷1.50 (m, 1H), 1.49 (s, 3H), 1.39 (d, 3H), 1.34 (s, 3H), 1.32 (d, 3H), 1.25 (m, 1H), 1.25 (d, 3H), 1.15 (d, 3H), 1.10 (d, 3H), 0.88 (t, 3H).

**Example 108**

**(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(1*H*-imidazo[4,5-*c*]pyridin-1-yl)-propylamino)-methylene]-erythromycin A**

and

**Example 109**

**(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(3*H*-imidazo[4,5-*c*]pyridin-3-yl)-propylamino)-methylene]-erythromycin A**

A solution of example 7 (0.050g) and intermediate 103 (0.034g) in anhydrous acetonitrile (1mL) was stirred at room temperature for 18h under nitrogen atmosphere. The solvent was evaporated under reduced pressure, the crude dissolved in anhydrous MeOH (2mL) then sodium cyanoborohydride (1M in THF, 0.037mL) and acetic acid (0.004mL) were added. After 18h the solvent was removed under reduced pressure, the residue dissolved in DCM (5mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by preparative TLC (DCM/MeOH/NH<sub>4</sub>OH 90/9/0.5) to give the title compound 108 (0.008g) and the title compound 109 (0.004g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (example 108): 9.11 (s, 1H), 8.44 (d, 1H), 8.08 (s, 1H), 7.47 (d, 1H), 4.41 (m, 1H), 4.28 (m, 1H), 4.14 (m, 1H), 3.05 (m, 1H), 3.00-2.90 (m, 2H), 2.31 (m, 1H), 2.08 (m, 1H), 1.95 (m, 1H), 1.09 (d, 3H).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (example 109): 8.90 (s, 1H), 8.45 (d, 1H), 8.16 (s, 1H), 7.70 (d, 1H), 4.48 (m, 1H), 4.37 (m, 1H), 4.15 (bs, 1H), 3.08 (m, 1H), 2.95 (m, 1H), 2.33 (m, 1H), 2.14 (m, 1H), 2.04 (m, 1H), 1.09 (d, 3H).

**Example 110**

**(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(1*H*-benzimidazol-1-yl)-propylamino)-methylene]-erythromycin A**

A solution of example 7 (0.050g) and intermediate 104 (0.025g) in anhydrous acetonitrile (1mL) was stirred at room temperature for 18h under nitrogen atmosphere. The solvent was evaporated under reduced pressure, the crude dissolved in anhydrous MeOH (2mL) then sodium cyanoborohydride (1M in THF, 0.037mL) and acetic acid (0.004mL) were added. After 18h the solvent was removed under reduced pressure, the residue dissolved in DCM (5mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH from 100/0 to 94/6) to give the title compound (0.021g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.00 (s, 1H), 7.80 (d, 1H), 7.48 (d, 1H), 7.40-7.20 (m, 2H), 4.38 (m, 1H), 4.24 (m, 1H), 4.10 (m, 1H), 3.05 (m, 1H), 3.03 (m, 1H), 2.98 (m, 1H), 2.32 (m, 1H), 2.02 (m, 1H), 1.93 (m, 1H), 1.09 (d, 3H).

**Example 111**

**(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(3H-imidazo[4,5-b]pyridin-3-yl)-propylamino)-methylene]-erythromycin A**

A solution of example 7 (0.050g) and intermediate 105 (0.034g) in anhydrous acetonitrile (1mL) was stirred at room temperature for 18h under nitrogen atmosphere. The solvent was evaporated under reduced pressure, the crude dissolved in anhydrous MeOH (2mL) then sodium cyanoborohydride (1M in THF, 0.037mL) and acetic acid (0.004mL) were added. After 18h the solvent was removed under reduced pressure, the residue dissolved in DCM (5mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH from 100/0 to 94/6) and by preparative TLC (eluting with: DCM/MeOH/NH<sub>4</sub>OH 90/9/0.5) to give the title compound (0.004g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.39 (dd, 1H), 8.21 (s, 1H), 8.05 (dd, 1H), 7.22 (dd, 1H), 4.43 (t, 2H), 4.15 (m, 1H), 3.04 (m, 1H), 2.32 (m, 1H), 1.10 (d, 3H).

**Example 112**

**(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(quinoxalin-2-ylsulfanyl)-propylamino)-methylene]-erythromycin A**

A solution of intermediate 106 (0.080g) in acetonitrile (3mL) and a 2N HCl aqueous solution (2mL) was heated to 40°C for 1h. The reaction mixture was cooled down to room temperature, then it was added dropwise to a solution of example 7 (0.090g) dissolved in anhydrous acetonitrile (3mL) keeping the pH of the solution in the range 6-7 by addition of saturated NaHCO<sub>3</sub> aqueous solution. The solution was stirred at room temperature overnight. Acetic acid was added to the mixture to reach pH 5-6 followed by sodium cyanoborohydride (1M in THF, 0.200mL). The reaction mixture was stirred for 5h at room temperature. After evaporating the solvent a saturated NaHCO<sub>3</sub> aqueous solution (10mL) was added and the product was extracted with DCM (4x15mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The residue was dissolved in MeOH (4mL) and stirred overnight. After evaporating the solvent the crude material was purified by flash chromatography (eluting with DCM/MeOH from 98/2 to 96/4) affording the title compound (0.050g).

m/z ([MH]<sup>+</sup>) = 829.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.57 (s, 1H), 7.99 (d, 1H), 7.96 (d, 1H), 7.69 (t, 1H), 7.60 (t, 1H), 5.71 (dd, 1H), 4.32 (d, 1H), 4.25 (m, 1H), 4.17 (m, 1H), 3.84 (q, 1H), 3.57 (m, 1H), 3.25 (m, 1H), 3.50-2.90 (m, 4H), 3.20-2.90 (m, 4H), 2.69 (s, 3H), 2.58 (m, 1H), 2.37 (s, 6H), 2.34 (m, 1H), 2.10-1.85 (m, 3H), 1.80-1.40 (m, 4H), 1.49 (s, 3H), 1.37 (d, 3H), 1.31 (d, 3H), 1.31 (s, 3H), 1.28 (m, 1H), 1.25 (d, 3H), 1.15 (d, 3H), 1.10 (d, 3H), 0.85 (t, 3H).

**Example 113**

**(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(4-phenyl-1H-imidazol-1-yl)-propylamino)-methylene]-erythromycin A**

A solution of example 7 (0.050g) and intermediate 107 (0.027g) in anhydrous acetonitrile (1mL) was stirred at room temperature for 18h under nitrogen atmosphere. The solvent was evaporated under reduced pressure, the crude dissolved in anhydrous MeOH (2mL) then sodium cyanoborohydride (1M in THF, 0.037mL) and acetic acid (0.004mL) were added.

5 After 18h the solvent was removed under reduced pressure, the residue dissolved in DCM (5mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by preparative TLC (eluting with: DCM/MeOH/NH<sub>4</sub>OH 90/9/0.5) to give the title compound (0.012g).

10 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.79 (d, 2H), 7.56 (m, 1H), 7.36 (m, 2H), 7.29 (d, 1H), 7.25 (m, 1H), 4.32 (m, 1H), 4.15 (m, 1H), 4.04 (m, 1H), 3.05 (m, 1H), 3.05-2.95 (m, 2H), 2.33 (m, 1H), 1.98 (m, 1H), 1.80 (m, 1H), 1.09 (d, 3H).

#### **Example 114**

15 **(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(4-pyridin-4-yl-1H-imidazol-1-yl)-ethylamino)-methylene]-erythromycin A**

A solution of intermediate 108 (0.060g) in acetonitrile (1.5mL) and a 3M HCl aqueous solution (1.5mL) was stirred at 70°C for 14h. The reaction mixture was allowed to reach room temperature, then it was added dropwise to a solution of example 7 (0.030g) dissolved in anhydrous acetonitrile (1mL) keeping the pH of the solution in the range 6-7 by addition of a saturated NaHCO<sub>3</sub> aqueous solution. The solution was stirred at room temperature for 4h. Acetic acid was added to the mixture to reach pH 5-6 followed by sodium cyanoborohydride (1M in THF, 0.150mL). The reaction mixture was stirred for 72h at room temperature. After evaporating the solvent a saturated NaHCO<sub>3</sub> aqueous solution (3mL) was added and the mixture was extracted with DCM (3x5mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The crude material was purified by flash chromatography (eluting with DCM/MeOH from 100/0 to 97/3) and by preparative TLC (eluting with: DCM/MeOH 90/10) to give the title compound (0.004g).

30 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.57 (d, 2H), 7.72 (d, 2H), 7.71 (m, 1H), 7.60 (m, 1H), 5.63 (dd, 1H), 4.27 (d, 1H), 4.19 (s, 1H), 4.18 (d, 1H), 4.12 (m, 2H), 3.85 (q, 1H), 3.55 (m, 1H), 3.32 (m, 1H), 3.24 (m, 1H), 3.16 (dd, 1H), 3.05 (m, 1H), 3.03 (m, 1H), 2.56 (m, 1H), 2.44 (m, 1H), 2.41 (s, 3H), 2.27 (s, 1H), 2.26 (s, 6H), 1.85 (m, 1H), 1.78 (m, 1H), 1.70÷1.63 (m, 2H), 1.55 (m, 1H), 1.48 (s, 3H), 1.41 (d, 3H), 1.31 (d, 3H), 1.24 (m, 1H), 1.24 (d, 3H), 1.23 (s, 3H), 1.14 (d, 3H), 1.09 (d, 3H), 0.81 (t, 3H).

#### **Example 115**

**(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(quinoxalin-2-ylsulfanyl)-ethylamino)-methylene]-erythromycin A**

40 A solution of intermediate 109 (0.067g) in acetonitrile (3mL) and a 2N HCl aqueous solution (2mL) was stirred overnight. Then, the reaction mixture was added dropwise to a solution of example 7 (0.090g) dissolved in anhydrous acetonitrile (3mL) keeping the pH of the solution in the range 6-7 by addition of saturated NaHCO<sub>3</sub> aqueous solution. The reaction mixture was

stirred at room temperature for 3h. Acetic acid was added to the mixture to reach pH 5-6 followed by sodium cyanoborohydride (1M in THF, 0.200mL). The reaction mixture was stirred for 5h at room temperature. After evaporating the solvent a saturated NaHCO<sub>3</sub> aqueous solution (10mL) was added and the mixture was extracted with DCM (4x15mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The residue was dissolved in MeOH (4mL) and stirred overnight. After evaporating the solvent the crude material was purified by flash chromatography (eluting with DCM/MeOH from 98/2 to 96/4) to give the title compound (0.076g).

m/z ([MH]<sup>+</sup>) = 815.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.55 (s, 1H), 7.99 (d, 1H), 7.93 (d, 1H), 7.68 (t, 1H), 7.60 (t, 1H), 5.68 (dd, 1H), 4.32 (d, 1H), 4.26 (d, 1H), 4.21 (m, 1H), 3.83 (q, 1H), 3.62-3.48 (m, 3H), 3.23 (m, 2H), 3.19 (dd, 1H), 3.10 (m, 1H), 3.04 (m, 1H), 2.74 (s, 3H), 2.58 (m, 1H), 2.48 (m, 1H), 2.35 (s, 1H), 2.29 (s, 6H), 1.91 (m, 1H), 1.80-1.67 (m, 3H), 1.55 (m, 1H), 1.49 (s, 3H), 1.35 (d, 3H), 1.30 (d, 3H), 1.34 (s, 3H), 1.26 (m, 1H), 1.25 (d, 3H), 1.14 (d, 3H), 1.09 (d, 3H), 0.86 (t, 3H).

#### **Example 116**

##### **(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(4-(thiophen-2-yl)-imidazol-1-yl)-propylamino)-methylene]-erythromycin A**

A solution of example 6 (0.040g) and intermediate 110 (0.033g) in anhydrous acetonitrile (1.5mL) was stirred at room temperature for 12h. After evaporating the solvent the residue was dissolved in anhydrous MeOH (1.5mL) and sodium cyanoborohydride (1M in THF, 0.030mL) and acetic acid (0.004mL) were added. The reaction mixture was stirred for 12h. The solvent was evaporated under vacuum, the residue dissolved in DCM (5mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x2mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The crude material was purified by flash chromatography (eluting with: DCM /MeOH 100/0, 98/2, 97/3) affording the title compound (0.025g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.52 (d, 1H), 7.18 (d, 1H), 7.27 (m, 1H), 7.16 (d, 1H), 7.02 (dd, 1H), 5.58 (dd, 1H), 4.31 (d, 1H), 4.25 (d, 1H), 4.14 (m, 1H), 4.12 (m, 1H), 4.02 (m, 1H), 3.86 (q, 1H), 3.56 (m, 1H), 3.20 (m, 1H), 3.10 (m, 1H), 3.04 (m, 1H), 2.93 (m, 2H), 2.68 (s, 3H), 2.60 (m, 1H), 2.50 (m, 1H), 2.32 (m, 1H), 2.30 (s, 6H), 2.05-1.85 (m, 3H), 1.80 (m, 1H), 1.70 (m, 2H), 1.60 (m, 1H), 1.49 (s, 3H), 1.39 (d, 3H), 1.34 (s, 3H), 1.32 (d, 3H), 1.25 (d+m, 3H+1H), 1.16 (d, 3H), 1.10 (d, 3H), 0.88 (t, 3H).

#### **Example 117**

##### **(11*S*,21*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(4-(thiophen-2-yl)-imidazol-1-yl)-propylamino)-methylene]-erythromycin A**

A solution of example 7 (0.750g) and intermediate 110 (0.300g) in anhydrous acetonitrile (15mL) was stirred at room temperature for 12h. After evaporating the solvent the residue was dissolved in anhydrous MeOH (15mL) and sodium cyanoborohydride (1M in THF, 0.728mL) and acetic acid (0.084mL) were added. The mixture was stirred overnight at room temperature. The solvent was evaporated under vacuum, the crude material dissolved in DCM

(50mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x20mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The crude material was purified by flash chromatography (eluting with: DCM \MeOH from 95\5 to 90\10) to give the title compound (0.872g, (21*S*) isomer 95% pure by NMR analysis).

5 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.52 (d, 1H), 7.18 (d, 1H), 7.27 (m, 1H), 7.16 (d, 1H), 7.02 (dd, 1H), 5.58 (dd, 1H), 4.31 (d, 1H), 4.25 (d, 1H), 4.14 (m, 1H), 4.12 (m, 1H), 4.02 (m, 1H), 3.86 (q, 1H), 3.56 (m, 1H), 3.20 (m, 1H), 3.10 (m, 1H), 3.04 (m, 1H), 2.93 (m, 2H), 2.68 (s, -OCH<sub>3</sub>), 2.60 (m, 1H), 2.50 (m, 1H), 2.32 (m, 1H), 2.30 (s, N(CH<sub>3</sub>)<sub>2</sub>), 2.05-1.85 (m, 3H), 1.80 (m, 1H), 1.70 (m, 2H), 1.60 (m, 1H), 1.49 (s, 3H), 1.39 (d, 3H), 1.34 (s, 3H), 1.32 (d, 3H), 1.25 (d+m, 3H+1H), 1.16 (d, 3H), 1.10 (d, 3H), 0.88 (t, 3H).

#### **Example 118**

##### **(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(6-methyl-2-oxo-1,3-benzoxazol-3(2H)-yl)-propylamino)-methylene]-erythromycin A**

15 A solution of example 7 (0.050g) and intermediate 111 (0.035g) in anhydrous acetonitrile (2mL) was stirred at 50°C for 6h. After cooling to room temperature solvent was evaporated, the residue dissolved in anhydrous MeOH (2mL) and sodium cyanoborohydride (1M in THF, 0.140mL) and acetic acid (0.010mL) were added. The mixture was stirred overnight at room temperature. The solvent was evaporated under vacuum, the residue dissolved in DCM

20 (50mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x20mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The crude material was purified by flash chromatography (eluting with: DCM \MeOH from 100\0 to 95\5) affording the title compound (0.020g).

25 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.20-6.80 (m, 3H), 5.66 (dd, 1H), 4.38 (d, 1H), 4.26 (d, 1H), 4.11 (s, 1H), 3.88 (m, 3H), 3.67 (m, 1H), 3.41 (m, 1H), 3.20-2.85 (m, 5H), 2.71 (s, 3H), 2.70 (bs, 6H), 2.59 (m, 1H), 2.41-2.35 (m, 1H+ 3H), 2.00-1.55 (m, 7H), 1.50 (s, 3H), 1.39 (d, 1H+3H), 1.32-1.27 (m, 3\*3H), 1.18 (d, 3H), 1.10 (d, 3H), 0.88 (t, 3H).

#### **Example 119**

##### **(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(2-pyridin-4-yl-1H-imidazol-1-yl)-ethylamino)-methylene]-erythromycin A**

30 A solution of intermediate 112 (0.060g) in acetonitrile (3mL) and a 3M HCl aqueous solution (3mL) was stirred at 80°C for 3 days. The reaction mixture was allowed to reach room temperature, then it was added dropwise to a solution of example 7 (0.050g) dissolved in

35 anhydrous acetonitrile (2mL) keeping the pH of the solution in the range 6-7 by addition of a saturated NaHCO<sub>3</sub> aqueous solution. The solution was stirred at room temperature for 24h. Acetic acid was added to the mixture to reach pH 5-6 followed by sodium cyanoborohydride (1M in THF, 0.070mL). The reaction mixture was stirred for 16h at room temperature. After evaporating the solvent a saturated NaHCO<sub>3</sub> aqueous solution (3mL) was added and the

40 product was extracted with DCM (3x5mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The crude material was dissolved in MeOH (1mL) and stirred



overnight. After evaporating the solvent the compound was purified by flash chromatography (eluting with DCM/MeOH from 100\0 to 97\3) to give the title compound (0.004g).

$m/z$  ( $[MH]^+$ ) = 798

5 **Example 120**

**(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-[3-(5-cyano-3,4-dimethylthien-2-yl)-1*H*-1,2,4-triazol-1-yl]-propylamino)-methylene]-erythromycin A**

10 A solution of example 7 (0.050g) and intermediate 113 (0.046g) in anhydrous acetonitrile (2mL) was stirred at room temperature for 18h under nitrogen atmosphere. The solvent was evaporated under reduced pressure, the residue dissolved in anhydrous MeOH (2mL) then sodium cyanoborohydride (1M in THF, 0.070mL) and acetic acid (0.009mL) were added. After 18h the solvent was removed under reduced pressure, the residue dissolved in DCM (5mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x3mL). The organic phase  
15 was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH from 100\0 to 94\6) to give the title compound (0.001g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.23 (s, 1H), 5.51 (dd, 1H), 4.38÷4.20 (m, 4H), 4.12(s, 1H), 3.86 (m, 1H), 3.55 (m, 1H), 3.18 (dd, 1H), 3.12÷3.00 (m, 2H), 2.98÷2.84 (m, 2H), 2.68 (s, 3H), 2.58  
20 (m, 1H), 2.52 (s, 3H), 2.44 (m, 1H), 2.37 (s, 3H), 2.32 (s, 1H), 2.27 (s, 6H), 2.12 (m, 1H), 2.02 (m, 1H), 1.92 (m, 1H), 1.81 (m, 1H), 1.74÷1.63 (m, 2H), 1.55 (m, 1H), 1.49 (s, 3H), 1.38 (d, 3H), 1.33 (s, 3H), 1.32 (d, 3H), 1.25(m, 1H), 1.25 (d, 3H), 1.15(d, 3H), 1.09 (d, 3H), 0.88 (t, 3H).

25 **Example 121**

**(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(quinolin-3-yl)-propylamino)-methylene]-erythromycin A**

30 A solution of example 7 (0.050g) and intermediate 114 (0.041g) in anhydrous acetonitrile (2mL) was stirred at room temperature for 18h under nitrogen atmosphere. The solvent was evaporated under reduced pressure, the residue dissolved in anhydrous MeOH (2mL) then sodium cyanoborohydride (1M in THF, 0.070mL) and acetic acid (0.009mL) were added. After 18h the solvent was removed under reduced pressure, the residue dissolved in DCM (5mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x3mL). The organic phase  
35 was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH from 100\0 to 94\6) to give the title compound (0.009g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.79 (d, 1H), 8.07 (d, 1H), 7.97 (d, 1H), 7.79 (d, 1H), 7.65 (t, 1H), 7.52 (t, 1H), 5.74 (dd, 1H), 4.32 (d, 1H), 4.25 (d, 1H), 4.17 (s, 1H), 3.85 (q, 1H), 3.55 (m, 1H), 3.22 (m, 1H), 3.11 (m, 1H), 3.04 (m, 1H), 3.02÷2.78 (m, 4H), 2.69 (s, 3H), 2.99 (m, 1H), 2.52  
40 (m, 1H), 2.34 (s, 1H), 2.32 (s, 6H), 1.94 (m, 1H), 1.89 (m, 2H), 1.88÷1.66 (m, 3H), 1.62÷1.50 (m, 1H), 1.49 (s, 3H), 1.39 (d, 3H), 1.32 (m, 6H), 1.25 (m, 1H), 1.25 (d, 3H), 1.16 (d, 3H), 1.10 (d, 3H), 0.88 (t, 3H).

**Example 122****(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-[4-(3-nitrophenyl)-1H-imidazol-1-yl]-propylamino)-methylene]-erythromycin A**

5 A solution of example 7 (0.050g) and intermediate 115 (0.026g) in anhydrous acetonitrile (1mL) was stirred at room temperature for 18h under nitrogen atmosphere. The solvent was evaporated under reduced pressure, the crude dissolved in anhydrous MeOH (2mL) then sodium cyanoborohydride (1M in THF, 0.037mL) and acetic acid (0.004mL) were added. After 18h the solvent was removed under reduced pressure, the residue dissolved in DCM (5mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH from 100\0 to 94\6) to give the title compound (0.007g).

15 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.62 (t, 1H), 8.17 (d, 1H), 8.05 (d, 1H), 7.60 (d, 1H), 4.15 (m, 2H), 4.09 (m, 1H), 4.05 (m, 1H), 3.02 (m, 1H), 3.04-2.92 (m, 2H), 2.33 (m, 1H), 2.05 (m, 1H), 1.98 (m, 1H), 1.12 (d, 3H).

**Example 123****(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(12-(2,3-dihydro-1,4-benzodioxin-6-yl)pyrrolidin-1-yl)]-methylene]-erythromycin A**

20 To a solution of example 7 (0.100g) in anhydrous acetonitrile intermediate 117 (0.066g) was added portionwise at room temperature under nitrogen atmosphere. After stirring overnight the solvent was removed under reduced pressure, the residue dissolved in MeOH (2.5mL) and sodium cyanoborohydride (1M in THF, 0.022mL) and acetic acid (0.013mL) added. The mixture was stirred overnight. The solvent was evaporated under vacuum, the residue dissolved in EtOAc (5mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x2mL) and brine (2mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The crude material was purified by flash chromatography (eluting with: DCM \MeOH from 100\0 to 97\3) affording the title compound (0.070g).

30 m/z ([MH]<sup>+</sup>) = 798

**Example 124****(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(5-methoxy-1H-pyrrolo[3,2-b]pyridin-1-yl)-propylamino)-methylene]-erythromycin A**

35 A solution of intermediate 118 (0.065g) in acetonitrile (2.5mL) and a 3M HCl aqueous solution (2.5mL) was stirred at 60°C for 8h. The reaction mixture was allowed to reach room temperature, then it was added dropwise to a solution of example 7 (0.040g) dissolved in anhydrous acetonitrile (1mL) keeping the pH of the solution in the range 6-7 by addition of a saturated NaHCO<sub>3</sub> aqueous solution. The mixture was stirred at room temperature for 24h. Acetic acid was added to reach pH 5-6 followed by sodium cyanoborohydride (1M in THF, 0.060mL). The reaction mixture was stirred overnight at room temperature. After evaporating the solvent a saturated NaHCO<sub>3</sub> aqueous solution (3mL) was added and the mixture was

extracted with DCM (3x5mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The crude material purified by flash chromatography (eluting with DCM/MeOH from 100\0 to 95\5) to give the title compound (0.014g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.66 (d, 1H), 7.25 (d, 1H), 6.62 (m, 1H), 6.51 (d, 1H), 4.40 (m, 1H), 4.30 (m, 1H), 4.15 (m, 1H), 4.00 (s, 3H), 3.03 (m, 1H), 3.05-2.88 (m, 2H), 2.30 (m, 1H), 2.06 (m, 1H), 1.96 (m, 1H), 1.10 (d, 3H).

#### **Example 125**

##### **(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-[3-(1,3-thiazol-2-yl)-1H-pyrazol-1-yl]-ethylamino)-methylene]-erythromycin A**

A solution of intermediate 119 (0.015g) in acetonitrile (1mL) and a 3M HCl aqueous solution (1mL) was stirred at room temperature for 16h and heated to 50°C for 8h. The reaction mixture was allowed to reach room temperature, then it was added dropwise to a solution of example 7 (0.033g) dissolved in anhydrous acetonitrile (1mL) keeping the pH of the solution in the range 6-7 by addition of saturated NaHCO<sub>3</sub> aqueous solution. The solution was stirred at room temperature overnight. Acetic acid was added to reach pH 5-6 followed by sodium cyanoborohydride (1M in THF, 0.025mL). The reaction mixture was stirred overnight at room temperature. After evaporating the solvent a saturated NaHCO<sub>3</sub> aqueous solution (3mL) was added and the mixture was extracted with DCM (3x5mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The residue was dissolved in MeOH (1mL) and stirred overnight. After evaporating the solvent the crude material was purified by flash chromatography (eluting with DCM/MeOH from 100\0 to 97\3) and by preparative LC (A/B from 80\20 to 10\90 in 20min) to give the title compound (0.014g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.80 (d, 1H), 7.69 (d, 1H), 7.27 (d, 1H), 6.76 (d, 1H), 5.63 (dd, 1H), 4.33 (m, 3H), 4.23 (m, 2H), 3.84 (m, 1H), 3.57 (m, 1H), 3.35 (m, 2H), 3.22 (m, 1H), 3.10-3.00 (m, 2H), 2.64-2.50 (m, 2H), 2.50 (s, 3H), 2.33 (s, 6H), 2.30 (s, 1H), 1.90 (m, 1H), 1.80-1.66 (m, 3H), 1.60-1.40 (m+s, 1H+3H), 1.40-1.20 (m, 4\*3H+1H), 1.14 (d, 3H), 1.09 (d, 3H), 0.86 (t, 3H).

#### **Example 126**

##### **(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(4-phenyl-1H-imidazol-1-yl)-ethylamino)-methylene]-erythromycin A**

A solution of intermediate 120 (0.023g) in acetonitrile (0.5mL) and a 3M HCl aqueous solution (0.7mL) was heated to 70°C for 24h. The reaction mixture was allowed to reach room temperature, then it was added dropwise to a solution of example 7 (0.039g) dissolved in anhydrous acetonitrile (0.5mL) keeping the pH of the solution in the range 6-7 by addition of saturated NaHCO<sub>3</sub> aqueous solution. The solution was stirred at room temperature for 6h. Acetic acid was added to reach pH 5-6 followed by sodium cyanoborohydride (1M in THF, 0.058mL). The reaction mixture was stirred overnight at room temperature. After evaporating the organic solvent the aqueous phase was extracted with EtOAc (3x5mL). The organic layer was washed with brine (3mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under

vacuum. The crude material was purified by flash chromatography (eluting with DCM/MeOH from 97\3 to 95\5) affording the title compound (0.026g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.80 (d, 2H), 7.58 (d, 1H), 7.45 (d, 1H), 7.36 (t, 2H), 7.21 (m, 1H), 4.21 (m, 1H), 4.14-4.07 (m, 2H), 3.30-3.20 (m, 2H), 3.07 (m, 1H), 2.29 (m, 1H), 1.10 (d, 3H).

#### Example 127

##### (11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(4-thien-2-yl-1*H*-imidazol-1-yl)-ethylamino)-methylene]-erythromycin A

A solution of intermediate **121** (0.088g) in acetonitrile (1.5mL) and a 3M HCl aqueous solution (1mL) was heated to 70°C for 24h. The reaction mixture was allowed to reach room temperature, then it was added dropwise to a solution of example **7** (0.100g) dissolved in anhydrous acetonitrile (1mL) keeping the pH of the solution in the range 6-7 by addition of saturated NaHCO<sub>3</sub> aqueous solution. The solution was stirred at room temperature for 6h. Acetic acid was added to reach pH 5-6 followed by sodium cyanoborohydride (1M in THF, 0.150mL). The reaction mixture was stirred overnight at room temperature. After evaporating the organic solvent the aqueous phase was extracted with EtOAc (3x5mL). The organic layer was washed with brine (3mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The crude material was purified by flash chromatography (eluting with DCM/MeOH from 97\3 to 95\5). The obtained compound was dissolved in MeOH (5mL) stirred overnight at room temperature. After evaporating the solvent, the residue was purified by flash chromatography (eluting with DCM/MeOH from 100\0 to 95\5) to give the title compound (0.034g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.54 (d, 1H), 7.32 (d, 1H), 7.28 (dd, 1H), 7.15 (dd, 1H), 7.01 (dd, 1H), 4.20 (m, 1H), 4.11-4.07 (m, 2H), 3.30-3.20 (m, 2H), 3.06 (m, 1H), 2.30 (m, 1H), 1.10 (d, 3H).

#### Example 128

##### (11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(quinolin-2-ylmethylamino)-methylene]-erythromycin A

A solution of example **6** (0.050g) and quinoline-2-carbaldehyde (0.015g) in anhydrous toluene (3mL) was heated to 110°C for 3h. The solution was allowed to reach room temperature and concentrated under reduced pressure. The residue was dissolved in MeOH (5mL) and palladium palladium (10wt. % on carbon powder, 0.020g) was added and the mixture stirred under hydrogen atmosphere (1 atm) for 1h. Filtration through a celite pad eluting with MeOH (10mL) and purification by flash chromatography (eluting with DCM/MeOH 90\10) gave the title compound (0.009g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.74 (s, 1H), 8.30 (d, 1H), 8.21 (d, 1H), 8.13 (td, 1H), 7.83 (t, 1H), 7.57 (t, 1H), 7.30 (t, 1H), 5.16 (bs, 1H), 3.12 (m, 1H), 2.93 (bs, 1H), 1.29 (d, 3H).

#### Example 129

##### (11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(quinolin-3-ylmethylamino)-methylene]-erythromycin A

A solution of example **6** (0.050g) and quinoline-3-carbaldehyde (0.016g) in anhydrous toluene (3mL) was stirred at 100°C for 15h. After evaporation of the solvent under reduced

pressure, the residue was dissolved in MeOH (1mL) and sodium cyanoborohydride (1M in THF, 0.060mL) and acetic acid (0.004mL) were added. The reaction mixture was stirred overnight at room temperature. After evaporating the solvent a saturated NaHCO<sub>3</sub> aqueous solution (3mL) was added and the mixture was extracted with DCM (3x5mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The crude material was purified by flash chromatography (eluting with DCM/MeOH 94/6) to give the title compound (0.007g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.94 (d, 1H), 8.23 (d, 1H), 8.09 (d, 1H), 7.82 (d, 1H), 7.67 (t, 1H), 7.53 (t, 1H), 4.29 (d, 1H), 4.28 (m, 2H), 4.18 (m, 1H), 3.07 (m, 1H), 2.48 (m, 1H), 1.10 (d, 3H).

#### **Example 130**

##### **(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(N-[3-(4-pyridin-3-yl-1H-imidazol-1-yl)-propylacetamido)-methylene]-erythromycin A**

To a solution of example 66 (0.010g) in anhydrous DCM (0.4mL) DMAP (0.050g) and acetyl chloride (0.030mL) were added portionwise over 4 days. Water (2mL) was added and the mixture was extracted with DCM (3x5mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The crude material was purified by flash chromatography (eluting with DCM/MeOH from 97/3 to 95/5). The compound was dissolved in MeOH (1mL) and stirred overnight. Solvent evaporation gave the title compound (0.002g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.97(s, 1H), 8.48 (d, 1H), 8.07 (d, 1H), 7.62 (s, 1H), 7.39 (s, 1H), 7.31 (m, 1H), 5.53 (bm, 1H), 4.35 (d, 1H), 4.29 (m, 1H), 4.15 (m, 1H), 4.01 (d, 1H), 3.83 (m, 1H), 3.72 (q, 1H), 3.65 (bs, 1H), 3.57-3.52 (m, 3H), 3.21 (m, 1H), 3.10 (m, 1H), 2.73 (m, 1H), 2.65-2.50 (m, 2H+3H), 2.39-2.22 (m, 2H+6H), 2.00 (s, 3H), 1.99 (m, 1H), 1.70-1.50 (m, 4H), 1.46 (s, 3H), 1.40 (d, 3H), 1.29-1.23 (m, 7H), 1.26 (s, 3H), 1.10 (d, 3H+3H), 0.95 (t, 3H).

#### **Example 131**

##### **(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(benzyl-carbamate)-methylene]-erythromycin A**

To a solution of example 7 (0.070g) in anhydrous DCM (2mL) cooled to 0°C TEA(0.090mL), DMAP (catalytic amount) and benzyl chloroformate (0.070g) were added under nitrogen atmosphere. The mixture was stirred at 0°C for 3h. After reaching room temperature a saturated NaHCO<sub>3</sub> aqueous solution (3mL) was added and the mixture was extracted with DCM (2x5mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH from 100/0 to 98/2). The obtained compound was dissolved in MeOH (1mL) and stirred at room temperature overnight. Solvent evaporation gave the title compound (0.002g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.40-7.20 (m, 5H), 5.81 (d, 1H), 5.16 (m, 1H), 5.08 (m, 1H), 4.80 (bm, 1H), 3.07 (m, 1H), 2.44 (m, 1H), 1.18 (d, 3H).

#### **Example 132**

**(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((quinolin-2-ylmethylene)-amino)-methylene]-erythromycin A**

A solution of example 6 (0.050g) and quinoline-2-carbaldehyde (0.015g) in anhydrous toluene (3mL) was heated to 110°C for 3h. The solution was allowed to reach room temperature and concentrated under reduced pressure. The residue was dissolved in MeOH (5mL) and stirred for 16h. Solvent evaporation gave the title compound (0.050g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.99 (d, 1H), 8.47 (d, 1H), 8.09 (d, 1H), 7.58 (s, 1H), 7.41 (s, 1H), 7.30 (m, 1H), 6.73 (d, 1H), 4.88 (dd, 1H), 4.67 (s, 1H), 3.08 (m, 1H), 2.41 (d, 1H), 1.16 (d, 3H).

**Example 133**

**(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-2-fluoro-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(quinoxalin-2-ylsulfanyl)-acetamido)-methylene]-erythromycin A**

To a solution of (quinoxalin-2-ylsulfanyl)-acetic acid (0.056g) in anhydrous DMF (4mL) under a nitrogen atmosphere HATU (0.097g) and DIPEA (0.053mL) were added. The reaction mixture was stirred at room temperature for 20 min then example 11 (0.160g) was added. The reaction mixture was stirred at room temperature for 6h then it was diluted with DCM (10mL) and washed with a 5% NaHCO<sub>3</sub> aqueous solution (10mL). The aqueous phase was extracted with DCM (3x10mL), the combined organic layers washed with a 5% NaHCO<sub>3</sub> aqueous solution (10mL), dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure. The residue was dissolved in MeOH (5mL) and stirred at room temperature overnight. After evaporating the solvent the crude material was purified by flash chromatography (DCM/MeOH 95/5) to give the title compound (0.126g).

m/z ([MH]<sup>+</sup>) = 847

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.63 (s, 1H), 8.20 (d, 1H), 7.99 (m, 2H), 7.72 (t, 1H), 7.65 (t, 1H), 5.47 (dd, 1H), 4.36 (d, 1H), 3.98 (s, 1H), 3.92 (d, 1H), 3.51 (m, 1H), 3.16 (m, 1H), 3.02 (m, 1H), 2.88 (m, 1H), 2.64 (s, 3H), 2.58 (m, 1H), 2.36 (m, 1H), 2.34 (s, 6H<sub>2</sub>), 2.10 (m, 1H), 2.03 (m, 1H), 1.97 (m, 1H), 1.73 (m, 4H), 1.60-1.40 (m, 8H), 1.23 (m, 4H), 1.15-1.01 (m, 9H), 0.90 (t, 3H).

**Example 134**

**(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-2-fluoro-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(2-hydroxy-4,5-dimethoxy-phenyl)-4-oxo-butyramido)-methylene]-erythromycin A**

To a solution of 4-(2-hydroxy-4,5-dimethoxy-phenyl)-4-oxo-butyric acid (0.031g) in anhydrous DMF (2mL) HATU (0.047g) and DIPEA (0.025mL) were added under nitrogen atmosphere. After stirring for 30min example 10 (0.070g) was added and the mixture stirred overnight. A 5% NaHCO<sub>3</sub> aqueous solution (3mL) was added and the mixture extracted with DCM (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure. The residue was dissolved in MeOH (3mL) and stirred overnight. After solvent evaporation the crude material was purified by flash chromatography (eluting with: DCM/MeOH/NH<sub>4</sub>OH from 100/0/0 to 85/15/0.2) to give the title compound (0.027g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 12.46 (s, 1H), 7.15 (s, 1H), 6.72 (d, 1H), 6.44 (s, 1H), 4.44 (m, 1H), 3.91 (s, 3H), 3.34 (s, 3H), 3.34 (m, 2H), 3.04 (m, 1H), 2.70-2.52 (m, 2H), 2.34 (m, 1H), 1.80 (d, 3H), 1.17 (d, 3H).

5 **Example 135**

**(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-2-fluoro-6-O-methyl-3-oxo-12,11-  
[oxycarbonyl-(4-(3,4-dimethoxy-phenyl)-4-oxo-butylramido)-methylene]-erythromycin A**

To a solution of 4-(3,4-dimethoxy-phenyl)-4-oxo-butylramide (0.029g) in anhydrous DMF (2mL) HATU (0.047g) and DIPEA (0.025mL) were added under nitrogen atmosphere. After stirring for 30min example 10 (0.070g) was added and the mixture stirred overnight. A 5% NaHCO<sub>3</sub> aqueous solution (3mL) was added and the mixture extracted with DCM (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure. The residue was dissolved in MeOH (3mL) and stirred overnight. After solvent evaporation the crude material was purified by flash chromatography (eluting with: DCM/MeOH/NH<sub>4</sub>OH from 100/0/0 to 85/15/0.2) to give the title compound (0.024g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.64 (d, 1H), 7.53 (m, 1H), 6.89 (d, 1H), 6.77 (d, 1H), 4.40 (t, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 3.35 (m, 2H), 3.04 (m, 1H), 2.70-2.55 (m, 2H), 2.34 (m, 1H), 1.81 (d, 3H), 1.17 (d, 3H).

20 **Example 136**

**(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-2-fluoro-6-O-methyl-3-oxo-12,11-  
[oxycarbonyl-(4-(4-methoxy-3-nitro-phenyl)-4-oxo-butylramido)-methylene]-  
erythromycin A**

To a solution of 4-(4-methoxy-3-nitro-phenyl)-4-oxo-butylramide (0.031g) in anhydrous DMF (2mL) HATU (0.047g) and DIPEA (0.025mL) were added under nitrogen atmosphere. After stirring for 30min example 10 (0.070g) was added and the mixture stirred overnight. A 5% NaHCO<sub>3</sub> aqueous solution (3mL) was added and the mixture extracted with DCM (2x3mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure. The residue was dissolved in MeOH (3mL) and stirred overnight. After solvent evaporation the crude material was purified by flash chromatography (eluting with: DCM/MeOH/NH<sub>4</sub>OH from 100/0/0 to 85/15/0.2) to give the title compound (0.030g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.49 (d, 1H), 8.20 (dd, 1H), 7.15 (d, 1H), 6.66 (d, 1H), 4.40 (t, 1H), 4.04 (s, 3H), 3.31 (m, 2H), 2.99 (m, 1H), 2.73 (m, 1H), 2.61 (m, 1H), 2.18 (m, 1H), 1.18 (d, 3H).

35 **Example 137**

**(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-2-fluoro-6-O-methyl-3-oxo-12,11-  
[oxycarbonyl-(2-(4-(pyridin-3-yl)-1H-imidazol-1-yl)-ethylamino)-methylene]-  
erythromycin A**

A solution of intermediate 51 (0.070g) in acetonitrile (2.5mL) and a 3M HCl aqueous solution (2.5mL) was heated to 80°C for 24h. The reaction mixture was allowed to reach room temperature, then it was added dropwise to a solution of example 10 (0.070g) dissolved in anhydrous acetonitrile (2mL) keeping the pH of the solution in the range 6-7 by addition of a

saturated NaHCO<sub>3</sub> aqueous solution. The mixture was stirred at room temperature overnight. Acetic acid was added to reach pH 5-6 followed by sodium cyanoborohydride (1M in THF, 0.150mL). The reaction mixture was stirred overnight at room temperature. After evaporating the solvent a saturated NaHCO<sub>3</sub> aqueous solution (3mL) was added and the mixture was extracted with DCM (2x5mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The crude material was purified by flash chromatography (eluting with DCM/MeOH/NH<sub>4</sub>OH from 100/0/0 to 80/20/0.2) to give the title compound (0.006g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 9.05 (d, 1H), 8.44 (d, 1H), 8.13 (m, 1H), 7.65 (d, 1H), 7.57 (d, 1H), 7.27 (m, 2H), 4.20-4.10 (m, 2H), 4.07 (bs, 1H), 3.40-3.25 (m, 2H), 2.87 (m, 1H), 2.32 (m, 1H), 1.81 (d, 3H), 1.08 (d, 3H).

#### **Example 138**

**(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-2-fluoro-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(4-(pyridin-3-yl)-imidazol-1-yl)-propylamino)-methylene]-erythromycin**

#### **A**

A solution of example 10 (0.070g) and intermediate 52 (0.035g) in anhydrous acetonitrile (3.5mL) was stirred at room temperature for 6h. After evaporating the solvent the residue was dissolved in anhydrous MeOH (3mL) and sodium cyanoborohydride (1M in THF, 0.051mL) and acetic acid (0.008mL) were added. The mixture was stirred overnight. The solvent was evaporated under vacuum, the residue dissolved in DCM (10mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (2x10mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH/NH<sub>4</sub>OH from 100/0/0 to 80/20/0.2) to give the title compound (0.012g).

m/z ([MH]<sup>+</sup>) = 830.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.99 (d, 1H), 8.46 (dd, 1H), 8.11 (dd, 1H), 7.63 (s, 1H), 7.40 (s, 1H), 7.30 (m, 1H), 5.45 (dd, 1H), 4.42 (d, 1H), 4.18 (m, 1H), 4.08 (m, 1H), 4.04 (m, 1H), 3.55 (m, 1H), 3.18 (dd, 1H), 3.11 (m, 1H), 3.00 (m, 1H), 2.92 (m, 1H), 2.95 (s, 3H), 2.95 (m, 1H), 2.58 (m, 1H), 2.52 (m, 1H), 2.30 (s, 6H), 1.95 (m, 2H), 1.83 (d, 3H), 1.57 (d, 3H), 1.7 (m, 1H), 1.68 (m, 1H), 1.60 (m, 1H), 1.33 (s, 3H), 1.26 (s, 3H), 1.25 (m, 1H), 1.25 (d, 3H), 1.16 (d, 3H), 1.09 (d, 3H), 0.92 (t, 3H).

#### **Example 139**

**(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-methyl-6-nitrophenyl)-ureido)-2-ethylamino)-methylene]-erythromycin A**

To a solution of example 13 (0.039g) in anhydrous DCM (2mL) cooled to -10°C a solution of 6-methyl-2-nitroisocyanate (0.010g) in anhydrous DCM (2mL) was added and the mixture was stirred at -10°C for 2h. The reaction mixture was quenched with a saturated NaHCO<sub>3</sub> aqueous solution (2mL), the aqueous phase was extracted with DCM (2mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH from 97/3 to 95/5) to give the title compound (0.010g).



<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.97 (bs, 1H), 7.78 (d, 1H), 7.44 (d, 1H), 7.15 (t, 1H), 6.23 (bs, 1H), 4.22 (s, 1H), 3.45 (m, 1H), 3.26-3.19 (m, 2H), 3.08 (m, 1H), 2.91 (m, 1H), 2.32 (s, 1H), 1.12 (d, 3H).

5 **Example 140**

**(11S,21R)-2'-O-Acetyl-3-Decladinosyl-11,12-dideoxy-6-O-allyl-3-oxo-12,11-[oxycarbonyl-(cyano)-methylene]-erythromycin A**

To a solution of intermediate **38** (0.33g) in DCM (30mL) Dess-Martin periodinane (0.300g) was added portionwise within 3h. A Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution (5% in a saturated NaHCO<sub>3</sub> aqueous solution, 20mL) was added and the mixture was stirred for 1h. The aqueous phase was  
10 extracted with DCM (2x50mL), the organic phase was washed with water (2x30mL), dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure. Purification of the crude material by flash chromatography (eluting with: DCM/MeOH/NH<sub>3</sub> 9.6\0.3\0.09) gave the title compound (0.13g).

15 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 5.69 (m, 1H), 5.43 (dd, 1H), 5.09 (m, 2H), 4.75 (m, 1H), 4.73 (s, 1H), 4.47 (d, 1H), 4.39 (d, 1H), 3.91 (q, 1H), 3.70 (m, 2H), 3.63 (m, 1H), 3.21 (m, 1H), 3.20 (s, 1H), 3.12 (m, 1H), 2.70 (m, 1H), 2.65 (m, 1H), 2.26 (s, 6H), 2.04 (s, 3H), 1.94 (m, 1H), 1.70 (m, 1H), 1.65 (m, 1H), 1.60 (s, 3H), 1.55 (m, 1H), 1.36 (d, 3H), 1.33 (s, 3H), 1.26 (d, 6H), 1.13 (d, 3H), 1.06 (d, 3H), 0.93 (t, 3H).

20

**Example 141**

**(11S,21R)-3-Decladinosyl-11,12-dideoxy-6-O-allyl-3-oxo-12,11-[oxycarbonyl-(cyano)-methylene]-erythromycin A**

A solution of example **140** (0.005g) in MeOH (0.5mL) was stirred at room temperature overnight. Solvent evaporation under reduced pressure gave the title compound (0.003g).

25 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 5.71 (m, 1H), 5.44 (dd, 1H), 5.08 (m, 2H), 4.72 (s, 1H), 4.43 (d, 1H), 4.40 (d, 1H), 3.94 (q, 1H), 3.72 (m, 2H), 3.62 (m, 1H), 3.20 (m, 4H), 2.68 (m, 1H), 2.52 (m, 1H), 2.29 (s, 6H), 1.94 (m, 1H), 1.81 (m, 1H), 1.65 (m, 1H), 1.60 (m, 1H), 1.61 (s, 3H), 1.42 (d, 3H), 1.35 (s, 3H), 1.34 (d, 3H), 1.26 (d, 3H), 1.12 (d, 3H), 1.08 (d, 3H), 0.93 (t, 3H).

30

**Example 142**

**(11S,21R,S)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-6-O-allyl-3-oxo-12,11-[oxycarbonyl-(benzhydrylideneamino)-methylene]-erythromycin A**

To a solution of intermediate **42** (0.528g) and EDC (0.35g) in DCM anhydrous (40mL) cooled to 0°C, DMSO (0.4mL) was added. After 10 min at 0°C, a solution of pyridinium trifluoroacetate (0.36g) in DCM (2mL) was slowly added. After 10min the ice bath was removed. Two further additions of EDC (0.35g each time), DMSO (0.4mL each time) and pyridinium trifluoroacetate (0.36g each time) were performed. The reaction mixture was  
35 quenched with water (50mL) and extracted with DCM (3x50mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum to give the title compound (0.520g).

40

TLC: DCM/MeOH/NH<sub>3</sub> 20\2\0.2 (R<sub>f</sub>=0.39).

**Example 143****(11S,21R,S)-2'-O-Acetyl-3-decladinosyl-11,12-dideoxy-6-O-allyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A**

A solution of example 142 (0.52g) in acetonitrile (66mL) and 1.2N HCl aqueous solution (154mL) was stirred at room temperature for 1h. After neutralising the mixture with solid Na<sub>2</sub>CO<sub>3</sub> and evaporating the solvent under vacuum, the mixture was extracted with DCM (3x50mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give the title compound (0.47g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 5.88 (dd, 1H), 5.70 (m, 1H), 5.13 (d, 1H), 4.75 (m, 1H), 4.57 (s, 1H), 4.44 (d, 1H), 4.38 (d, 1H), 3.91 (q, 1H), 3.75 (q, dd), 3.61 (m, 1H), 3.50 (m, 1H), 3.24 (m, 1H), 3.08 (m, 1H), 2.70 (m, 1H), 2.64 (m, 1H), 2.46 (bs, 1H), 2.26 (s, 6H), 2.18 (m, 6H), 1.60-1.40 (m, 5H), 1.40-1.20 (m, 13H), 1.15 (d, 3H), 1.08 (d, 3H), 0.88 (t, 3H).

**Example 144****(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-allyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A**

A solution of example 143 (0.002g) in MeOH (0.3mL) was stirred at room temperature overnight. Solvent evaporation under reduced pressure gave the title compound (0.002g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 5.82 (dd, 1H), 5.73 (m, 1H), 5.14 (d, 1H), 5.02 (d, 1H), 4.54 (s, 1H), 4.40 (d, 1H), 4.38 (d, 1H), 3.93 (q, 1H), 3.76 (m, 1H), 3.62 (m, 1H), 3.52 (m, 1H), 3.24 (m, 1H), 3.21 (m, 1H), 3.09 (m, 1H), 2.66 (m, 1H), 2.50 (m, 1H), 2.47 (m, 1H), 2.28 (s, 6H), 1.95 (m, 1H), 1.85 (m, 2H), 1.80-0.80 (several m, 27H).

m/z ([MH]<sup>+</sup>) = 653.

**Example 145****(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-quinolin-2-ylsulfanyl)-ethylamino)-methylene]-erythromycin A**

To a solution of quinolin-2-thiol (0.008g) in anhydrous DMF (0.500mL) sodium hydride (1.2mg) was added and the mixture stirred at room temperature for 15min then intermediate 24 (0.025g) was added and the reaction mixture stirred at 60°C for 5h. The reaction mixture was diluted with DCM (3mL) and washed with a saturated NaHCO<sub>3</sub> aqueous solution (1mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH 98/2) to give a compound that was dissolved in MeOH (1mL) and stirred at room temperature overnight.

Solvent evaporation under reduced pressure gave the title compound (0.010g).

LC/MS analysis (mobile phase: A/B from 90/10 to 10/90 in 10 min, 10/90 for 2 min, mass range 150-1300 amu); retention time: 8.7 min, m/z ([MH]<sup>+</sup>) = 815.

**Example 146****(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-benzothiazol-2-ylsulfanyl)-ethylamino)-methylene]-erythromycin A**

- To a solution of benzothiazole-2-thiol (0.009g) in anhydrous DMF (0.500mL) sodium hydride (1.2mg) was added and the mixture stirred at room temperature for 15min then intermediate **24** (0.025g) was added and the reaction mixture stirred at 60°C for 5h. The reaction mixture was diluted with DCM (3mL), washed with a saturated NaHCO<sub>3</sub> aqueous solution (1mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure. The crude material was purified by flash chromatography (eluting with: DCM/MeOH 98/2) to give a compound that was dissolved in MeOH (1mL) and stirred at room temperature overnight. Solvent evaporation under reduced pressure gave the title compound (0.012g).
- LC/MS analysis (mobile phase: A/B from 90/10 to 10/90 in 10 min, 10/90 for 2 min, mass range 150-1300 amu): retention time: 8.5 min, m/z ([MH]<sup>+</sup>) = 821.

#### Example 147

#### 3-Pyridin-3-yl-acrylamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

- To 3-pyridin-3-yl-acrylic acid (1.3mg) a solution of HATU (0.003g) in anhydrous DMF (0.050mL) and DIPEA (0.002mL) in anhydrous DMF (0.050mL) were added, followed by a solution of example **6** (0.005g) in anhydrous DMF (0.050mL). The reaction mixture was stirred at room temperature for 18 h, then it was diluted with DCM (0.350mL), washed with a 5% NaHCO<sub>3</sub> aqueous solution (0.300mL), then passed through a phase-separation syringe. The aqueous phase was extracted with DCM (0.250mL) and the collected organic extracts evaporated under vacuum. The crude material was dissolved in DCM (0.700mL), loaded on SCX-cartridge (250mg, loading 0.28mmol/g, previously washed with 4mL of MeOH), washed with MeOH (3.5mL), then the product eluted with NH<sub>3</sub> (0.25M solution in MeOH, 1mL), followed by MeOH (0.7mL). The collected fractions were left in the NH<sub>3</sub>/MeOH solution overnight. After evaporating the solvent the title compound (0.002g) was obtained.
- LC/MS analysis (mobile phase: A/B from 90/10 to 10/90 in 10 min, 10/90 for 5 min; mass range 150-1200 amu): retention time: 5 min, m/z ([MH]<sup>+</sup>) = 758.

- Examples **148-312**:

#### Example 148

#### 3-Benzo[1,3]dioxol-5-yl-acrylamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

35

#### Example 149

#### (4-Methyl-2-oxo-2*H*-chromen-7-yloxy)-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

#### Example 150

#### [(Furan-2-carbonyl)-amino]-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 151**

3-(Thiophen-2-ylsulfanyl)-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

5

**Example 152**

(Benzo[1,3]dioxol-5-ylamino)-phenyl-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

10

**Example 153**

{[3-(2-Chloro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino}-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

15

**Example 154**

2-Acetylamino-3-(6-methyl-1*H*-indol-3-yl)-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

20

**Example 155**

2-Acetylamino-3-(5-methyl-1*H*-indol-3-yl)-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

25

**Example 156**

(*E*)-3-(2,3-Dimethoxy-pyrimidin-5-yl)-acrylamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 157**

30

[5-(2-Methoxy-phenyl)-4-phenyl-4*H*-[1,2,4]triazol-3-ylsulfanyl]-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 158**

35

2-(4-Methyl-[1,2,3]thiadiazol-5-ylsulfanyl)-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 159**

40

(7-Methyl-thieno[3,2-*d*]pyrimidin-4-ylsulfanyl)-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 160**

[5-(2-Chloro-phenyl)-pyrimidin-4-ylsulfanyl]-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin

A

**Example 161**

(4-Methyl-5-quinolin-6-yl-4*H*-[1,2,4]triazol-3-ylsulfanyl)-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 162**

[(5-Bromo-furan-2-carbonyl)-amino]-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 163**

[(Thiophene-2-carbonyl)-amino]-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 164**

(4-Hydroxy-2-methyl-pyridin-3-yloxy)-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 165**

3-(1*H*-Indol-3-yl)-acrylamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 166**

4-Oxo-4-thiophen-2-yl-butylamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 167**

4-(4,5-Dimethoxy-2-nitro-phenyl)-4-oxo-butylamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin

A

**Example 168**

4-(2-Methoxy-phenyl)-4-oxo-butylamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 169**

4-Oxo-4-pyridin-3-yl-butyramide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 170

5 4-(4-Methylsulfanyl-phenyl)-4-oxo-butyramide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 171

10 3-(1*H*-Imidazol-4-yl)-acrylamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 172

15 4-Thien-2-yl- butyramide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 173

3-(1*H*-Indol-3-yl)-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

20 Example 174

(Pyridin-4-ylsulfanyl)-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 175

25 (Pyrimidin-2-ylsulfanyl)-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 176

30 [(Pyridine-3-carbonyl)-amino]-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 177

35 (*Z*)-3-Pyridin-4-yl-acrylamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 178

(*E*)-3-Pyridin-4-yl-acrylamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

40 Example 179

[2-(6-Methyl-pyridin-2-yl)-1-phenyl-ethylsulfanyl]-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

5 Example 180

[(4-Oxo-4*H*-chromene-2-carbonyl)-amino]-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

10 Example 181

3-(1,4-Dioxo-3,4-dihydrophthalazin-2(1*H*)-yl)-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

15 Example 182

(4-Methyl-[1,2,3]thiadiazol-5-ylsulfanyl)-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 183

20 (Benxothiazol-2-ylsulfanyl)-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 184

25 3-(1*H*-Imidazol-4-yl)-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 185

30 3-Pyridin-3-yl-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 186

35 [(4-Methoxy-quinoline-2-carbonyl)-amino]-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 187

(3-Phenyl-[1,2,4]oxadiazol-5-ylamino)-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

40 Example 188

[4-(6-Oxo-1,4,5,6-tetrahydro-pyridazin-3-yl)-phenoxy]-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

5 Example 189

3-(5-Methyl-1*H*-indol-3-yl)-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 190

10 4-(2,3-dioxo-2,3-dihydro-1*H*-indol-5-yl)-butyramide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 191

15 3-(1,3,8-Trimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropteridin-6-yl)-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 192

20 3-(4-Oxo-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 193

25 [4-(1,3-Dimethyl-6-oxo-2-thioxo-2,3,6,9-tetrahydro-1*H*-purin-8-yl)-phenoxy]-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 194

30 2-Benzoylamino-3-(1*H*-indol-3-yl)-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 195

35 3-Phenyl-4-(pyridin-2-ylcarbamoyl)-butyramide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 196

40 3-Benzo[1,3]dioxol-5-yl-2-benzoylamino-acrylamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 197



3-(3-Phenyl-ureido)-3-thiophen-3-yl-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 198

5 3-(Furan-2-yl)-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 199

10 2-Hydroxy-3-(1*H*-indol-3-yl)-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 200

15 3-(5-Phenyl-1*H*-pyrrol-2-yl)-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 201

4-Oxo-4-thiophen-2-yl-butyramide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

20 Example 202

(4-Methyl-pyrimidin-2-ylsulfanyl)-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 203

25 4-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-phenyl]-butyramide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 204

30 4-(2-Methyl-1-oxo-1,2-dihydroisoquinolin-3-yl)-butyramide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 205

35 3-[3-(4-Methoxyphenyl)-1,2,4-oxadiazol-5-yl]-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 206

40 (4,6-Dimethyl-pyrimidin-2-ylsulfanyl)-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 207

3-(2-Oxo-1,3-benzoxazol-3(2H)-yl)-propionamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

5 Example 208

4-(1,3-Dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)-butyramide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

10 Example 209

2-Formylamino-2-(1H-indol-3-yl)-propionamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 210

15 4-Methyl-2-[(2-methylsulfanyl-pyridine-3-carbonyl)-amino]-pentanamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 211

20 (3,5,6-Trichloro-pyridin-2-yloxy)-acetamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 212

25 (5-Phenyl-pyrimidin-2-ylsulfanyl)-acetamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 213

30 3-(6-Bromo-benzo[1,3]dioxol-5-yl)-2-cyano-acrylamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 214

35 3-[3-(4-Nitrophenyl)-1,2,4-oxadiazol-5-yl]-propionamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 215

40 3-(1,3-Benzothiazol-2-yl)-propionamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 216

3-(3-Pyridin-2-yl-1,2,4-oxadiazol-5-yl)-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin  
A

5 Example 217

4-(3-Pyridin-4-yl-1,2,4-oxadiazol-5-yl)-butyramide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 218

10 4-(3-Pyridin-2-yl-1,2,4-oxadiazol-5-yl)-butyramide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 219

15 3-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 220

20 4-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-butyramide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 221

25 4-(1,3-Benzodioxol-5-yl)-butyramide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 222

30 4-[3-(5-Oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-6-yl)-1,2,4-oxadiazol-5-yl]-butyramide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 223

35 4-[3-(3-Nitrophenyl)-1,2,4-oxadiazol-5-yl]-butyramide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 224

40 3-Pyrimidin-2-yl-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 225

4-(2,3-Dihydro-1,4-benzodioxin-6-yl)-butyramide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 226

5 3-[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]-propionamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 227

10 4-(1H-Indol-3-yl)-butyramide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 228

15 (5-Trifluoromethyl-pyridin-2-ylsulfanyl)-acetamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 229

20 (Quinolin-8-yloxy)-acetamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 230

3-(Quinoxalin-2-ylsulfanyl)-propionamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

25 Example 231

(2-Pyridin-2-yl-6-trifluoromethyl-pyrimidin-4-ylsulfanyl)-acetamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

30 Example 232

3-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-acrylamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

35 Example 233

3-Pyridin-2-yl-acrylamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 234

40 (2,2-Dimethyl-4-oxo-chroman-7-yloxy)-acetamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 235**

[3-(5-Oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidin-6-yl)-[1,2,4]oxadiazol-5-ylmethylsulfanyl]-acetamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 236**

(5,6,7,8-Tetrahydro-quinazolin-4-ylsulfanyl)-acetamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 237**

Benzo[1,3]dioxol-5-yl-propionamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 238**

[5-(5-Nitro-furan-2-yl)-[1,3,4]oxadiazol-2-ylsulfanyl]-acetamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 239**

(Pyridin-2-ylsulfanyl)-acetamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 240**

[(2-Phenoxy-pyridine-3-carbonyl)-amino]-acetamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 241**

3-Benzo[1,3]dioxol-5-yl-2-cyano-acrylamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 242**

(Benzenesulfonyl-pyridin-2-yl-amino)-acetamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 243**

(3-Chloro-4-methyl-2-oxo-2H-chromen-7-yloxy)-acetamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 244**

(5-Bromo-4-hydroxy-2-methyl-pyridin-3-yloxy)-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

5 Example 245

(4-Methyl-4*H*-[1,2,4]triazol-3-ylsulfanyl)-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 246

10 (2,2,5-Trimethyl-4-oxo-chroman-7-yloxy)-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 247

15 3-(1-*tert*-Butyl-3,5-dimethyl-1*H*-pyrazol-4-yl)-acrylamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 248

20 (1*H*-Indol-3-yl)-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 249

25 Thien-3-yl-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 250

(2-Phenyl-1,3-thiazol-4-yl)-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

30

Example 251

(1*H*-Indol-3-yl)-oxo-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

35 Example 252

Thien-2-yl-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 253

40 1*H*-Imidazol-4-yl-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 254

1,3-Benzodioxol-5-yl-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

5 Example 255

(2-Pyrazin-2-yl-1,3-thiazol-4-yl)-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 256

10 (5-Bromo-1*H*-indol-3-yl)-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 257

15 1-Benzothien-3-yl-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 258

Pyridin-2-yl-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

20

Example 259

(1-Methyl-1*H*-indol-3-yl)-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

25 Example 260

(5-Fluoro-1*H*-indol-3-yl)-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 261

30 (5-Methoxy-1*H*-indol-3-yl)-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 262

35 (4-Oxo-3,4-dihydrophthalazin-1-yl)-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 263

40 (5-Methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 264

(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-acetamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

5 Example 265

(5-Methoxy-2-methyl-1H-indol-3-yl)-acetamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 266

10 (2-Methyl-1H-indol-3-yl)-acetamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 267

15 (5-Methyl-2-phenyl-1,3-oxazol-4-yl)-acetamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 268

20 (6-Hydroxy-pyridazin-3-yl)-(4-methoxy-phenyl)-acetamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 269

25 (5-Methyl-1-phenyl-1H-pyrazol-4-yl)-acetamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 270

(5-Methyl-2-phenyl-1,3-thiazol-4-yl)-acetamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

30 Example 271

Pyridin-3-yl-acetamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 272

35 (5-Hydroxy-1H-indol-3-yl)-acetamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 273

40 1-Benzothien-4-yl-acetamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 274



2-Furyl-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 275

5 (2,3-Dimethyl-1*H*-indol-5-yl)-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 276

10 4-(1,3-Benzothiazol-2-yl)-butyramide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 277

15 3-(2-Methyl-1*H*-indol-3-yl)-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 278

20 4-[3-(5-Nitrothien-3-yl)-1,2,4-oxadiazol-5-yl]-butyramide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 279

3-(1-Methyl-1*H*-benzimidazol-2-yl)-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

25 Example 280

3-(4,6-Dimethoxypyrimidin-2-yl)-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 281

30 (6,7-Dmethoxy-isoquinolin-4-yl)-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 282

35 [3-(2-Chlorophenyl)-5-methyl-isoxazol-4-yl]-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Example 283

40 [4-(4-Oxo-1,2,3-benzotriazin-3(4*H*)-yl)phenyl]-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 284**

[2-(2,4-Difluorophenyl)-1,3-thiazol-4-yl]-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

5 **Example 285**

[2-({[(5-Methyl-1,3,4-thiadiazol-2-yl)thio]acetyl}amino)-1,3-thiazol-4-yl]-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

10 **Example 286**

(2-{{[(Pyridin-2-ylthio)acetyl]amino}-1,3-thiazol-4-yl}-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

15 **Example 287**

(2-{{[(Phenylthio)acetyl]amino}-1,3-thiazol-4-yl}-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

20 **Example 288**

{2-[(4-Bromobenzoyl)amino]-1,3-thiazol-4-yl}-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

25 **Example 289**

{2-[(3-Chlorobenzoyl)amino]-1,3-thiazol-4-yl}-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

30 **Example 290**

{2-[(2-Chlorobenzoyl)amino]-1,3-thiazol-4-yl}-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

35 **Example 291**

[1-(6-Chloropyridazin-3-yl)-1*H*-indol-3-yl]-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

40 **Example 292**

[2-(4-Chlorophenyl)-1,3-thiazol-4-yl]-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 293**

[4-(4-Bromophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl]-acetamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 294**

(2-Oxo-1,3-benzoxazol-3(2H)-yl)-acetamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 295**

[2-(4-Methoxyphenyl)-1,3-thiazol-4-yl]-acetamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 296**

3-Furyl-acetamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 297**

(4-Methyl-2-thioxo-1,3-thiazol-3(2H)-yl)-acetamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 298**

[2-(Benzoylamino)-1,3-thiazol-4-yl]-acetamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 299**

[4-(3,5-Dimethyl-1H-pyrazol-1-yl)phenyl]-acetamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 300**

[4-(1H-Pyrazol-1-yl)phenyl]-acetamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 301**

1-Benzofuran-4-yl-acetamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 302**

2-Acetyl-amino-3-(1H-indol-3-yl)-propionamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 303**

3-(1,3-Benzodioxol-5-yl)-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 304**

3-(1*H*-Benzimidazol-2-yl)-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 305**

3-(6-Ethylsulfanyl-pyridin-3-yl)-acrylamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 306**

[4-Oxo-2-(1*H*-tetrazol-5-yl)-4*H*-chromen-7-yloxy]-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 307**

3-(1-Oxoisoquinolin-2(1*H*)-yl)-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 308**

2-Benzoylamino-3-(1*H*-imidazol-4-yl)-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 309**

3-Thien-2-yl-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 310**

(3-Methyl-6-trifluoromethyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylsulfanyl)-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 311**

[(2-*p*-Tolysulfanyl-pyridine-3-carbonyl)-amino]-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 312**

**3-[3-(3-nitrophenyl)-1,2,4-oxadiazol-5-yl]-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin**  
**A**

- 5 Examples **148-312** were obtained starting from example **6** (5 mg) by following the same procedure as reported for Example **147**.  
 The name and amount of starting material (i.e carboxylic acid) and LC/MS analysis (retention time and m/z) of examples **148-312** are reported in the Table 1.

10

Table 1

Ex. N	Carboxylic acid	Amount (mg)	Ret. time (min)	Mass analysis m/z [MH] <sup>+</sup>
<b>148</b>	3-Benzo[1,3]dioxol-5-yl-acrylic acid	1.7	6.1 6.8	801
<b>149</b>	(4-Methyl-2-oxo-2 <i>H</i> -chromen-7-yloxy)-acetic acid	2.1	6,7	843
<b>150</b>	[(Furan-2-carbonyl)-amino]-acetic acid	1.5	4,9	778
<b>151</b>	3-(Thiophen-2-ylsulfanyl)-propionic acid	1.7	6,5 7,3	797
<b>152</b>	(Benzo[1,3]dioxol-5-ylamino)-phenyl-acetic acid	2.4	7,0 7,4	880
<b>153</b>	{[3-(2-Chloro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino}-acetic acid	2.7	6,3	903
<b>154</b>	2-Acetylamino-3-(6-methyl-1 <i>H</i> -indol-3-yl)-propionic acid	2.3	5,9	869
<b>155</b>	2-Acetylamino-3-(5-methyl-1 <i>H</i> -indol-3-yl)-propionic acid	2.3	5,8	869
<b>156</b>	( <i>E</i> )-3-(2,3-Dimethoxy-pyrimidin-5-yl)-acrylic acid	1.9	6,7 7,4	819

157	[5-(2-Methoxy-phenyl)-4-phenyl-4 <i>H</i> -[1,2,4]triazol-3-ylsulfanyl]-acetic acid	3.0	7,6	950
158	2-(4-Methyl-[1,2,3]thiadiazol-5-ylsulfanyl)-propionic acid	1.8	7,3 8,0	813
159	(7-Methyl-thieno[3,2- <i>d</i> ]pyrimidin-4-ylsulfanyl)-acetic acid	2.2	7,5 8,1	849
160	[5-(2-Chloro-phenyl)-pyrimidin-4-ylsulfanyl]-acetic acid	2.5	7,9 8,4	889
161	(4-Methyl-5-quinolin-6-yl-4 <i>H</i> -[1,2,4]triazol-3-ylsulfanyl)-acetic acid	2.6	6,3	909
162	[(5-Bromo-furan-2-carbonyl)-amino]-acetic acid	2.2	6,6	856
163	[(Thiophene-2-carbonyl)-amino]-acetic acid	1.6	6,3	794
164	(4-Hydroxy-2-methyl-pyridin-3-yloxy)-acetic acid	1.6	5,2	792
165	3-(1 <i>H</i> -Indol-3-yl)-acrylic acid	1.7	7,3 8,1	796
166	4-Oxo-4-thiophen-2-yl-butyric acid	1.7	6,0 6,6	793
167	4-(4,5-Dimethoxy-2-nitro-phenyl)-4-oxo-butyric acid	2.5	6,3 6,8	892
168	4-(2-Methoxy-phenyl)-4-oxo-butyric acid	1.9	6,3	817
169	4-Oxo-4-pyridin-3-yl-butyric acid	1.6	5,0 5,4	788

170	4-(4-Methylsulfanyl-phenyl)-4-oxo-butyric acid	2,0	6,6	833
171	3-(1 <i>H</i> -Imidazol-4-yl)-acrylic acid	1,1	4,54 4,87	747
172	4-Thien-2-yl- butyric acid	1,4	6,47 7,17	779
173	3-(1 <i>H</i> -Indol-3-yl)- propionic acid	1,6	6,17 6,66	798
174	(Pyridin-4-ylsulfanyl)-acetic acid	1,4	5,02 5,50	778
175	(Pyrimidin-2-ylsulfanyl)-acetic acid	1,4	5,59	779
176	[(Pyridine-3-carbonyl)-amino]-acetic acid	1,5	4,51	789
177	( <i>Z</i> )-3-Pyridin-4-yl-acrylic acid	1,2	5,05 5,64	758
178	( <i>E</i> )-3-Pyridin-4-yl-acrylic acid	1,2	5,02 5,62	758
179	[2-(6-Methyl-pyridin-2-yl)-1-phenyl-ethylsulfanyl]-acetic acid	2,4	6,95 7,45	896
180	[(4-Oxo-4 <i>H</i> -chromene-2-carbonyl)-amino]-acetic acid	2,0	5,32	856
181	3-(1,4-Dioxo-3,4-dihydrophthalazin-2(1 <i>H</i> )-yl)-propionic acid	1,9	4,54	843
182	(4-Methyl-[1,2,3]thiadiazol-5-ylsulfanyl)-acetic acid	1,6	5,88 6,39	799

183	(Benxothiazol-2-ylsulfanyl)-acetic acid	1,8	6,81 7,17	834
184	3-(1 <i>H</i> -Imidazol-4-yl)-propionic acid	1,2	4,39 4,59	749
185	3-Pyridin-3-yl-propionic acid	1,2	4,96 5,42	760
186	[(4-Methoxy-quinoline-2-carbonyl)-amino]-acetic acid	2,1	6,4	869
187	(3-Phenyl-[1,2,4]oxadiazol-5-ylamino)-acetic acid	1,8	6,27	827
188	[4-(6-Oxo-1,4,5,6-tetrahydro-pyridazin-3-yl)-phenoxy]-acetic acid	2,0	5,32	857
189	3-(5-Methyl-1 <i>H</i> -indol-3-yl)-propionic acid	1,7	6,51 7,00	812
190	4-(2,3-dioxo-2,3-dihydro-1 <i>H</i> -indol-5-yl)-butyric acid	1,9	5,38 5,80	842
191	3-(1,3,8-Trimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropteridin-6-yl)-propionic acid	2,4	4,60 4,92	903
192	3-(4-Oxo-4,7-dihydro-3 <i>H</i> -pyrrolo[2,3- <i>d</i> ]pyrimidin-5-yl)-propionic acid	1,7	4,47	816
193	[4-(1,3-Dimethyl-6-oxo-2-thioxo-2,3,6,9-tetrahydro-1 <i>H</i> -purin-8-yl)-phenoxy]-acetic acid	2,8	6,56 6,88	955
194	2-Benzoylamino-3-(1 <i>H</i> -indol-3-yl)-propionic acid	2,5	6,5	917
195	3-Phenyl-4-(pyridin-2-ylcarbamoyl)-butyric acid	2,3	6,31 6,62	893



196	3-Benzo[1,3]dioxol-5-yl-2-benzoylamino-acrylic acid	2,6	6,53	920
197	3-(3-Phenyl-ureido)-3-thiophen-3-yl-propionic acid	2,4	6,64	899
198	3-(Furan-2-yl)-propionic acid	1,2	5,91 6,45	749
199	2-Hydroxy-3-(1 <i>H</i> -indol-3-yl)-propionic acid	1,7	5,96	814
200	3-(5-Phenyl-1 <i>H</i> -pyrrol-2-yl)-propionic acid	1,8	7,13 7,48	824
201	4-Oxo-4-thiophen-2-yl-butyric acid	1,5	5,86 6,42	793
202	(4-Methyl-pyrimidin-2-ylsulfanyl)-acetic acid	1,5	5,53 5,85	793
203	4-[2-(1,3-Dioxo-1,3-dihydro-2 <i>H</i> -isoindol-2-yl)-phenyl]-butyric acid	2,6	6,64 7,16	918
204	4-(2-Methyl-1-oxo-1,2-dihydroisoquinolin-3-yl)-butyric acid	2,0	5,76	854
205	3-[3-(4-Methoxyphenyl)-1,2,4-oxadiazol-5-yl]-propionic acid	2,0	6,51 7,10	857
206	(4,6-Dimethyl-pyrimidin-2-ylsulfanyl)-acetic acid	1,6	5,74 6,10	807
207	3-(2-Oxo-1,3-benzoxazol-3(2 <i>H</i> )-yl)-propionic acid	1,7	5,95 6,36	816
208	4-(1,3-Dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1 <i>H</i> -purin-8-yl)-butyric acid	2,2	4,60 4,92	875

209	2-Formylamino-2-(1 <i>H</i> -indol-3-yl)-propionic acid	1,9	5,6	841
210	4-Methyl-2-[(2-methylsulfanyl-pyridine-3-carbonyl)-amino]-pentanoic acid	2,3	6,60 6,92	891
211	(3,5,6-Trichloro-pyridin-2-yloxy)-acetic acid	2,1	7,41 7,81	864
212	(5-Phenyl-pyrimidin-2-ylsulfanyl)-acetic acid	2,0	6,76 7,07	855
213	3-(6-Bromo-benzo[1,3]dioxol-5-yl)-2-cyano-acrylic acid	2,4	7,19 7,84	904
214	3-[3-(4-Nitrophenyl)-1,2,4-oxadiazol-5-yl]-propionic acid	2,2	6,75 7,29	872
215	3-(1,3-Benzothiazol-2-yl)-propionic acid	1,7	6,09 6,56	816
216	3-(3-Pyridin-2-yl-1,2,4-oxadiazol-5-yl)-propionic acid	1,80	6,27	828
217	4-(3-Pyridin-4-yl-1,2,4-oxadiazol-5-yl)-butyric acid	1,9	6,57 7,23	842
218	4-(3-Pyridin-2-yl-1,2,4-oxadiazol-5-yl)-butyric acid	1,9	6,45 7,05	842
219	3-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-propionic acid	2,1	8,55 9,15	861
220	4-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-butyric acid	2,2	8,68 9,34	875
221	4-(1,3-Benzodioxol-5-yl)-butyric acid	1,7	7,71 8,43	817

222	4-[3-(5-Oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyrimidin-6-yl)-1,2,4-oxadiazol-5-yl]-butyric acid	2,5	5,97 6,51	917
223	4-[3-(3-Nitrophenyl)-1,2,4-oxadiazol-5-yl]-butyric acid	2,3	8,07 8,73	886
224	3-Pyrimidin-2-yl-propionic acid	1,3	5,55	761
225	4-(2,3-Dihydro-1,4-benzodioxin-6-yl)-butyric acid	1,8	7,59 8,31	831
226	3-[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]-propionic acid	2,1	8,13 8,78	862
227	4-(1H-Indol-3-yl)-butyric acid	1,7	7,77 8,43	812
228	(5-Trifluoromethyl-pyridin-2-ylsulfanyl)-acetic acid	1,9	8,06 8,43	846
229	(Quinolin-8-yloxy)-acetic acid	2,0	6,93	812
230	3-(Quinoxalin-2-ylsulfanyl)-propionic acid	1,9	7,82	843
231	(2-Pyridin-2-yl-6-trifluoromethyl-pyrimidin-4-ylsulfanyl)-acetic acid	2,6	7,95 8,25	924
232	3-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-acrylic acid	2,1	8,31 9,27	860
233	3-Pyridin-2-yl-acrylic acid	1,2	6,27 7,05	758
234	(2,2-Dimethyl-4-oxo-chroman-7-yloxy)-acetic acid	2,1	7,48 7,90	859

235	[3-(5-Oxo-2,3-dihydro-5 <i>H</i> -thiazolo[3,2- <i>a</i> ]pyrimidin-6-yl)-[1,2,4]oxadiazol-5-ylmethylsulfanyl]-acetic acid	2,7	6,27 6,74	935
236	(5,6,7,8-Tetrahydro-quinazolin-4-ylsulfanyl)-acetic acid	1,8	7,23 7,71	833
237	Benzo[1,3]dioxol-5-yl-propionic acid	1,6	7,65 8,37	799
238	[5-(5-Nitro-furan-2-yl)-[1,3,4]oxadiazol-2-ylsulfanyl]-acetic acid	2,2	7,34 7,70	880
239	(Pyridin-2-ylsulfanyl)-acetic acid	1,4	7,05	778
240	[(2-Phenoxy-pyridine-3-carbonyl)-amino]-acetic acid	2,2	7,11	881
241	3-Benzo[1,3]dioxol-5-yl-2-cyano-acrylic acid	1,8	7,82	826
242	(Benzenesulfonyl-pyridin-2-yl-amino)-acetic acid	2,4	7,05	901
243	(3-Chloro-4-methyl-2-oxo-2 <i>H</i> -chromen-7-yloxy)-acetic acid	2,2	7,95 8,36	877
244	(5-Bromo-4-hydroxy-2-methyl-pyridin-3-yloxy)-acetic acid	2,2	5,67	870
245	(4-Methyl-4 <i>H</i> -[1,2,4]triazol-3-ylsulfanyl)-acetic acid	1,4	5,37 5,61	782
246	(2,2,5-Trimethyl-4-oxo-chroman-7-yloxy)-acetic acid	2,2	7,95	873
247	3-(1- <i>tert</i> -Butyl-3,5-dimethyl-1 <i>H</i> -pyrazol-4-yl)-acrylic acid	1,8	7,36 8,20	831

248	(1 <i>H</i> -Indol-3-yl)-acetic acid	1,4	7,17	784
249	Thien-3-yl-acetic acid	1,2	5,7 6,4	751
250	(2-Phenyl-1,3-thiazol-4-yl)-acetic acid	1,8	6,8 7,2	828
251	(1 <i>H</i> -Indol-3-yl)-oxo-acetic acid	1,6	6,5	798
252	Thien-2-yl-acetic acid	1,2	6,0 6,7	751
253	1 <i>H</i> -Imidazol-4-yl-acetic acid	1,3	4,3	735
254	1,3-Benzodioxol-5-ylacetic acid	1,5	5,9	789
255	(2-Pyrazin-2-yl-1,3-thiazol-4-yl)-acetic acid	1,8	5,5	830
256	(5-Bromo-1 <i>H</i> -indol-3-yl)-acetic acid	2, 1	6,5 7,0	862
257	1-Benzothien-3-yl-acetic acid	1,6	6,8	801
258	Pyridin-2-yl-acetic acid	1,4	5,1	746
259	(1-Methyl-1 <i>H</i> -indol-3-yl)-acetic acid	1,6	6,6	798
260	(5-Fluoro-1 <i>H</i> -indol-3-yl)-acetic acid	1,6	6,1 6,5	802

261	(5-Methoxy-1 <i>H</i> -indol-3-yl)-acetic acid	1,7	5,8	814
262	(4-Oxo-3,4-dihydrophthalazin-1-yl)-acetic acid	1,7	5	813
263	(5-Methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2 <i>H</i> )-yl)-acetic acid	1,5	4,6	793
264	(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1 <i>H</i> -pyrazol-4-yl)-acetic acid	2,0	5,4	855
265	(5-Methoxy-2-methyl-1 <i>H</i> -indol-3-yl)-acetic acid	1,8	6	828
266	(2-Methyl-1 <i>H</i> -indol-3-yl)-acetic acid	1,6	6,2 6,6	798
267	(5-Methyl-2-phenyl-1,3-oxazol-4-yl)-acetic acid	1,8	6,7	826
268	(6-Hydroxy-pyridazin-3-yl)-(4-methoxy-phenyl)-acetic acid	2,1	5,5	869
269	(5-Methyl-1-phenyl-1 <i>H</i> -pyrazol-4-yl)-acetic acid	1,8	6,0 6,3	825
270	(5-Methyl-2-phenyl-1,3-thiazol-4-yl)-acetic acid	1,9	7,1	842
271	Pyridin-3-yl-acetic acid	1,2	4,8	746
272	(5-Hydroxy-1 <i>H</i> -indol-3-yl)-acetic acid	1,6	5	800
273	1-Benzothien-4-yl-acetic acid	1,6	6,7	801

274	2-Furyl-acetic acid	1,1	5,7	732
275	(2,3-Dimethyl-1 <i>H</i> -indol-5-yl)-acetic acid	1,7	6,4 7,0	812
276	4-(1,3-Benzothiazol-2-yl)-butyric acid	1,8	6,4 7,0	830
277	3-(2-Methyl-1 <i>H</i> -indol-3-yl)-propionic acid	1,7	6,5 7,0	812
278	4-[3-(5-Nitrothien-3-yl)-1,2,4-oxadiazol-5-yl]-butyric acid	2,3	6,8 7,4	892
279	3-(1-Methyl-1 <i>H</i> -benzimidazol-2-yl)-propionic acid	1,7	5,7	813
280	3-(4,6-Dimethoxypyrimidin-2-yl)-propionic acid	1,7	5,9	821
281	(6,7-Dmethoxy-isoquinolin-4-yl)-acetic acid	2,0	5,4	856
282	[3-(2-Chlorophenyl)-5-methyl-isoxazol-4-yl]-acetic acid	2,1	6,8 7,3	860
283	[4-(4-Oxo-1,2,3-benzotriazin-3(4 <i>H</i> )-yl)phenyl]-acetic acid	2,3	6,4 6,9	890
284	[2-(2,4-Difluorophenyl)-1,3-thiazol-4-yl]-acetic acid	2,1	7,2	864
285	[2-({[(5-Methyl-1,3,4-thiadiazol-2-yl)thio]acetyl} amino)-1,3-thiazol-4-yl]-acetic acid	2,7	5,5	939
286	(2-{{[(Pyridin-2-ylthio)acetyl]amino}-1,3-thiazol-4-yl)-acetic acid	2,5	6,1	918

287	(2-{[(Phenylthio)acetyl]amino}-1,3-thiazol-4-yl)-acetic acid	2,5	6,6	917
288	{2-[(4-Bromobenzoyl)amino]-1,3-thiazol-4-yl}acetic acid	2,8	6,9	949
289	{2-[(3-Chlorobenzoyl)amino]-1,3-thiazol-4-yl}-acetic acid	2,4	6,8	905
290	{2-[(2-Chlorobenzoyl)amino]-1,3-thiazol-4-yl}-acetic acid	2,4	6,3	905
291	[1-(6-Chloropyridazin-3-yl)-1 <i>H</i> -indol-3-yl]-acetic acid	2,4	6,9	896
292	[2-(4-Chlorophenyl)-1,3-thiazol-4-yl]-acetic acid	2,1	7,5	862
293	[4-(4-Bromophenyl)-5-oxo-4,5-dihydro-1 <i>H</i> -1,2,4-triazol-1-yl]-acetic acid	2,4	6,3	906
294	(2-Oxo-1,3-benzoxazol-3(2 <i>H</i> )-yl)-acetic acid	1,7	6,1 6,4	802
295	[2-(4-Methoxyphenyl)-1,3-thiazol-4-yl]-acetic acid	2,0	6,8	858
296	3-Furyl-acetic acid	1,0	5,6	735
297	(4-Methyl-2-thioxo-1,3-thiazol-3(2 <i>H</i> )-yl)-acetic acid	1,6	5,8	798
298	[2-(Benzoylamino)-1,3-thiazol-4-yl]-acetic acid	2,2	6,2	871
299	[4-(3,5-Dimethyl-1 <i>H</i> -pyrazol-1-yl)phenyl]-acetic acid	1,9	6,2 6,7	839



300	[4-(1 <i>H</i> -Pyrazol-1-yl)phenyl]-acetic acid	1,7	5,9	811
301	1-Benzofuran-4-yl-acetic acid	1,4	6,5	785
302	2-Acetylamino-3-(1 <i>H</i> -indol-3-yl)-propionic acid	2,0	5,63 5,71	855
303	3-(1,3-Benzodioxol-5-yl)-propionic acid	1,6	6,28 6,76	803
304	3-(1 <i>H</i> -Benzimidazol-2-yl)-propionic acid	1,6	5,55	799
305	3-(6-Ethylsulfanyl-pyridin-3-yl)-acrylic acid	1,7	6,55 7,34	818
306	[4-Oxo-2-(1 <i>H</i> -tetrazol-5-yl)-4 <i>H</i> -chromen-7-yloxy]-acetic acid	2,4	4,88	897
307	3-(1-Oxoisoquinolin-2(1 <i>H</i> )-yl)-propionic acid	1,8	6,72 6,92	826
308	2-Benzoylamino-3-(1 <i>H</i> -imidazol-4-yl)-propionic acid	2,1	5,07	868
309	3-Thien-2-yl-propionic acid	1,3	6,30 6,89	765
310	(3-Methyl-6-trifluoromethyl-3 <i>H</i> -imidazo[4,5- <i>b</i> ]pyridin-2-ylsulfanyl)-acetic acid	2,4	7,96	900
311	[(2- <i>p</i> -Tolysulfanyl-pyridine-3-carbonyl)-amino]-acetic acid	2,5	7,57 7,84	911
312	3-[3-(3-nitrophenyl)-1,2,4-oxadiazol-5-yl]-propionic acid	2,2	7,92 8,53	872

**Example 313****(2R)-2-Amino-3-(1H-indol-3-yl)-propionamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A**

To (2R)-tert-butoxycarbonylamino-3-(1H-indol-3-yl)-propionic acid (0.0025g) a solution of HATU (0.003g) in anhydrous DMF (0.050mL) and DIPEA (0.002mL) in anhydrous DMF (0.050mL) were added, followed by a solution of example 6 (0.005g) in anhydrous DMF (0.050mL). The reaction mixture was stirred at room temperature for 18h, then it was diluted with DCM (0.350mL), washed with a 5% NaHCO<sub>3</sub> aqueous solution (0.300mL), then passed through a phase-separation syringe. The aqueous phase was extracted with DCM (0.250mL) and the collected organic extracts evaporated under vacuum. The residue was dissolved in a 10% TFA solution in anhydrous DCM (0.300mL) and the mixture stirred for 1.5h. The solution was diluted with EtOAc (0.400mL) then solvents evaporated under reduced pressure. The crude material was dissolved in DCM (0.700mL), loaded on SCX-cartridge (100mg, loading 0.75mmol/g, previously washed with 4mL of MeOH), washed with MeOH (4mL), then the product eluted with NH<sub>3</sub> (0.25M solution in MeOH, 1.5mL), followed by MeOH (2mL) and solvents evaporating under vacuum. The residue was dissolved in MeOH (1.7mL) and stirred overnight at room temperature. After evaporating the solvent the title compound (0.001g) was obtained.

LC/MS analysis (mobile phase: A/B from 90/10 to 10/90 in 10 min, 10/90 for 3 min; mass range 150-1000 amu): retention time: 4.95 min, m/z ([MH]<sup>+</sup>) = 813.

Examples 314-320:

**Example 314**

**(2S)-2-Amino-3-(1-methyl-1H-imidazol-5-yl)-propionamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A**

**Example 315**

**(2R)-2-Amino-3-(1,3-thiazol-4-yl)-propionamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A**

**Example 316**

**(2S)-2-Amino-3-(1,3-thiazol-4-yl)-propionamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A**

**Example 317**

**(2R)-2-Amino-3-(1H-imidazol-5-yl)-propionamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A**

**Example 318**

(2R)-2-Amino-3-pyridin-3-yl-propionamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 319**

5 (2S)-2-Amino-3-(1-methyl-1H-imidazol-4-yl)-propionamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 320**

10 (2S)-2-Amino-3-pyridin-2-yl-propionamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Examples 314-320 were obtained starting from example 6 (5 mg) by following the same procedure as reported for Example 313.

15 The name and amount of starting material (i.e carboxylic acid) and LC/MS analysis (retention time and m/z) of examples 314-320 are reported in the table 2.

**Table 2**

Ex. N	Carboxylic acid	Amount (mg)	Ret. time (min)	Mass analysis m/z [MH] <sup>+</sup>
314	(2S)-2-[( <i>tert</i> -butoxycarbonyl)amino]-3-(1-methyl-1H-imidazol-5-yl)-propionic acid	2,2	5,55	778
315	(2R)-2-[( <i>tert</i> -butoxycarbonyl)amino]-3-(1,3-thiazol-4-yl)-propionic acid	2,2	4,05	781
316	(2S)-2-[( <i>tert</i> -butoxycarbonyl)amino]-3-(1,3-thiazol-4-yl)-propionic acid	2,2	4,22 4,83	781
317	(2R)-2-[( <i>tert</i> -butoxycarbonyl)amino]-3-(1H-imidazol-5-yl)-propionic acid	2,1	3,51 4,16	764
318	(2R)-2-[( <i>tert</i> -butoxycarbonyl)amino]-3-pyridin-3-yl-propionic acid	2,2	3,98 4,70	775
319	(2S)-2-[( <i>tert</i> -butoxycarbonyl)amino]-3-(1-methyl-1H-imidazol-4-yl)-propionic acid	2,2	4,05 4,41	778

320	(2 <i>S</i> )-2-[( <i>tert</i> -butoxycarbonyl)amino]-3-pyridin-2-yl-propionic acid	2,2	4,11 4,77	775
-----	-------------------------------------------------------------------------------------	-----	--------------	-----

**Example 321****(2*S*)-2-Amino-3-pyridin-4-yl-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A**

5 To (2*S*)-2-[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}-3-pyridin-4-yl-propionic acid (0.0032g) a solution of HATU (0.003g) in anhydrous DMF (0.050mL) and DIPEA (0.002mL) in anhydrous DMF (0.050mL) were added, followed by a solution of example 6 (0.005g) in anhydrous DMF (0.050mL). The reaction mixture was stirred at room temperature for 18h, then it was diluted with DCM (0.350mL), washed with a 5% NaHCO<sub>3</sub> aqueous solution  
10 (0.300mL), then passed through a phase-separation syringe. The aqueous phase was extracted with DCM (0.250mL) and the collected organic extracts evaporated under vacuum. The residue was dissolved in anhydrous DMF (0.350mL) then piperazinomethyl polystyrene resin (0.030g, loading 1.39 mmol/g) was added and the mixture stirred for 2.5 days. The mixture was filtered and the resin rinsed with DCM (0.400mL), DMF (0.400mL) and DCM  
15 (0.200mL) and the filtrates evaporated under reduced pressure.

The crude material was dissolved in DCM (0.700mL), loaded on SCX-cartridge (100mg, loading 0.75mmol/g, previously washed with 4mL of MeOH), washed with MeOH (4mL), then the product eluted with NH<sub>3</sub> (0.25M solution in MeOH, 1.5mL), followed by MeOH (2mL) and solvents evaporating under vacuum. The residue was dissolved in MeOH (1.7mL)  
20 and stirred overnight at room temperature. After evaporating the solvent the title compound (0.001g) was obtained.

LC/MS analysis (mobile phase: A/B from 90/10 to 10/90 in 10 min, 10/90 for 3 min; mass range 150-1000 amu): retention time: 3.98/4.70 min, m/z ([MH]<sup>+</sup>) = 775.

25 Examples 322-327:

**Example 322****(2*S*)-2-Amino-3-{1-[(benzyloxy)methyl]-1*H*-imidazol-5-yl}-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A**

30

**Example 323****(2*S*)-2-Amino-3-(1-benzyl-1*H*-imidazol-4-yl)-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A**

35

**Example 324**

(2S)-2-Amino-3-(1H-imidazol-4-yl)-propionamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 325**

5 (2S)-2-Amino-3-{1-[(benzyloxy)methyl]-1H-imidazol-4-yl}-propionamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 326**

10 (3S)-3-Amino-4-(1H-indol-3-yl)-butyramide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

**Example 327**

15 (2R)-2-Amino-3-pyridin-4-yl-propionamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(amino)-methylene]-erythromycin A

Examples 322-327 were obtained starting from example 6 (5 mg) by following the same procedure as reported for Example 321.

20 The name and amount of starting material (i.e carboxylic acid) and LC/MS analysis (retention time and m/z) of examples 322-327 are reported in the table 3.

**Table 3**

Ex. N	Carboxylic acid	Amount (mg)	Ret. time (min)	Mass analysis m/z [MH] <sup>+</sup>
322	(2S)-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-3-{1-[(benzyloxy)methyl]-1H-imidazol-5-yl}-propionic acid	4,1	5,66	884
323	(2S)-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-3-(1-benzyl-1H-imidazol-4-yl)-propionic acid	3,8	5,01 5,61	854
324	(2S)-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-3-(1H-imidazol-4-yl)-propionic acid	3,1	3,92 4,28	764

<b>325</b>	(2 <i>S</i> )-2-{{[(9 <i>H</i> -fluoren-9-ylmethoxy)carbonyl]amino}-3-{1-[(benzyloxy)methyl]-1 <i>H</i> -imidazol-4-yl}}-propionic acid	4,1	5,67	884
<b>326</b>	(3 <i>S</i> )-3-{{[(9 <i>H</i> -fluoren-9-ylmethoxy)carbonyl]amino}-4-(1 <i>H</i> -indol-3-yl)-butyric acid	3,6	5,07 5,43	827
<b>327</b>	(2 <i>R</i> )-2-{{[(9 <i>H</i> -fluoren-9-ylmethoxy)carbonyl]amino}-3-pyridin-4-yl-propionic acid	3,2	3,87 4,70	775

**Example 328****(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-*O*-methyl-3-oxo-12,11-[oxycarbonyl-(benzoyl-ureido)-methylene]-erythromycin A**

- 5 To a solution of example 6 (0.005g) in anhydrous THF (0.100mL) a solution of benzoyl isocyanate (2.2mg) in anhydrous THF (0.300mL) was added. The reaction mixture was heated at 60°C for 24h. After cooling to room temperature PS-Trisamine resin (loading 3.62mmol/g, 0.030g) was added and reacted at 60°C for 24h. After cooling to room temperature the mixture was filtered and the resin rinsed with THF (2x0.240mL), DCM
- 10 (2x0.240mL), THF (4x0.170mL) and the filtrate evaporated. The residue was dissolved in MeOH (1mL) and reacted at room temperature overnight. After evaporating the solvent the title compound (0.003g) was obtained.

LC/MS analysis (mobile phase: A/B from 90/10 to 10/90 in 10 min, 10/90 for 2 min; retention time: 6.08/6.51min, m/z ([MH]<sup>+</sup>) = 774.

15

Examples 329-398:

**Example 329****(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-*O*-methyl-3-oxo-12,11-[oxycarbonyl-(phenyl-ureido)-methylene]-erythromycin A**

20

**Example 330****(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-*O*-methyl-3-oxo-12,11-[oxycarbonyl-((2,6-dichloropyridin-4-yl)-ureido)-methylene]-erythromycin A**

25

**Example 331****(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-*O*-methyl-3-oxo-12,11-[oxycarbonyl-((3,5-dimethylisoxazol-4-yl)-ureido)-methylene]-erythromycin A**

**Example 332**

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((pyridin-3-yl)-ureido)-methylene]-erythromycin A

5

**Example 333**

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2,2,4,4-tetrafluoro-4H-1,3-benzodioxin-6-yl)-ureido)-methylene]-erythromycin A

10

**Example 334**

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-(N,N-dimethylamino)phenyl)-ureido)-methylene]-erythromycin A

**Example 335**

15

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-nitrophenyl)-ureido)-methylene]-erythromycin A

**Example 336**

20

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((3-nitrophenyl)-ureido)-methylene]-erythromycin A

**Example 337**

25

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-nitrophenyl)-ureido)-methylene]-erythromycin A

**Example 338**

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((3,5-dinitrophenyl)-ureido)-methylene]-erythromycin A

30

**Example 339**

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-methyl-2-nitrophenyl)-ureido)-methylene]-erythromycin A

**Example 340**

35

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-methyl-4-nitrophenyl)-ureido)-methylene]-erythromycin A

**Example 341**

40

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-methyl-5-nitrophenyl)-ureido)-methylene]-erythromycin A

**Example 342**

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-methyl-3-nitrophenyl)-ureido)-methylene]-erythromycin A

Example 343

5 (11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-methyl-3-nitrophenyl)-ureido)-methylene]-erythromycin A

Example 344

10 (11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-methyl-6-nitrophenyl)-ureido)-methylene]-erythromycin A

Example 345

15 (11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((5-chloro-2-nitrophenyl)-ureido)-methylene]-erythromycin A

Example 346

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-chloro-4-nitrophenyl)-ureido)-methylene]-erythromycin A

20 Example 347

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-chloro-3-nitrophenyl)-ureido)-methylene]-erythromycin A

Example 348

25 (11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-chloro-2-nitrophenyl)-ureido)-methylene]-erythromycin A

Example 349

30 (11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-fluoro-3-nitrophenyl)-ureido)-methylene]-erythromycin A

Example 350

35 (11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-fluoro-5-nitrophenyl)-ureido)-methylene]-erythromycin A

Example 351

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-methoxy-5-nitrophenyl)-ureido)-methylene]-erythromycin A

40 Example 352

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-methoxy-4-nitrophenyl)-ureido)-methylene]-erythromycin A



**Example 353**

**(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-methoxy-2-nitrophenyl)-ureido)-methylene]-erythromycin A**

5

**Example 354**

**(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-methoxyphenyl)-ureido)-methylene]-erythromycin A**

10

**Example 355**

**(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((3-methoxyphenyl)-ureido)-methylene]-erythromycin A**

**Example 356**

15

**(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-methoxyphenyl)-ureido)-methylene]-erythromycin A**

**Example 357**

20

**(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((3,4-dimethoxyphenyl)-ureido)-methylene]-erythromycin A**

**Example 358**

25

**(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2,4-dimethoxyphenyl)-ureido)-methylene]-erythromycin A**

**Example 359**

**(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2,5-dimethoxyphenyl)-ureido)-methylene]-erythromycin A**

30

**Example 360**

**(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((3,5-dimethoxyphenyl)-ureido)-methylene]-erythromycin A**

**Example 361**

35

**(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2,6-dimethoxyphenyl)-ureido)-methylene]-erythromycin A**

**Example 362**

40

**(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((1,3-benzodioxol-5-yl)-ureido)-methylene]-erythromycin A**

**Example 363**

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-methoxy-5-methylphenyl)-ureido)-methylene]-erythromycin A

Example 364

5 (11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-ethoxyphenyl)-ureido)-methylene]-erythromycin A

Example 365

10 (11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-ethoxyphenyl)-ureido)-methylene]-erythromycin A

Example 366

15 (11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-phenoxyphenyl)-ureido)-methylene]-erythromycin A

Example 367

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-phenoxyphenyl)-ureido)-methylene]-erythromycin A

20 Example 368

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((3-phenoxyphenyl)-ureido)-methylene]-erythromycin A

Example 369

25 (11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((3-(cyclopentyloxy)-4-methoxyphenyl)-ureido)-methylene]-erythromycin A

Example 370

30 (11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((5-chloro-2-methoxyphenyl)-ureido)-methylene]-erythromycin A

Example 371

35 (11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((3-chloro-4-methoxyphenyl)-ureido)-methylene]-erythromycin A

Example 372

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((5-chloro-2,4-dimethoxyphenyl)-ureido)-methylene]-erythromycin A

40 Example 373

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-(trifluoromethoxy)phenyl)-ureido)-methylene]-erythromycin A

**Example 374**

**(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-(trifluoromethoxy)phenyl)-ureido)-methylene]-erythromycin A**

5

**Example 375**

**(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-(difluoromethoxy)phenyl)-ureido)-methylene]-erythromycin A**

10

**Example 376**

**(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-(difluoromethoxy)phenyl)-ureido)-methylene]-erythromycin A**

**Example 377**

15

**(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-(methylthio)phenyl)-ureido)-methylene]-erythromycin A**

**Example 378**

20

**(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((3-(methylthio)phenyl)-ureido)-methylene]-erythromycin A**

**Example 379**

25

**(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-(methylthio)phenyl)-ureido)-methylene]-erythromycin A**

**Example 380**

**(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-[(trifluoromethyl)thio]phenyl)-ureido)-methylene]-erythromycin A**

30

**Example 381**

**(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-acetylphenyl)-ureido)-methylene]-erythromycin A**

**Example 382**

35

**(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((3-acetylphenyl)-ureido)-methylene]-erythromycin A**

**Example 383**

40

**(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-cyanophenyl)-ureido)-methylene]-erythromycin A**

**Example 384**

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((3-cyanophenyl)-ureido)-methylene]-erythromycin A

Example 385

5 (11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((3-trifluoromethyl)-phenyl)-ureido)-methylene]-erythromycin A

Example 386

10 (11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-chlorophenyl)-ureido)-methylene]-erythromycin A

Example 387

15 (11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((3-chlorophenyl)-ureido)-methylene]-erythromycin A

Example 388

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-chlorophenyl)-ureido)-methylene]-erythromycin A

20 Example 389

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((3,4-dichlorophenyl)-ureido)-methylene]-erythromycin A

Example 390

25 (11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-fluorophenyl)-ureido)-methylene]-erythromycin A

Example 391

30 (11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((benzyl)-ureido)-methylene]-erythromycin A

Example 392

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-methoxybenzyl)-ureido)-methylene]-erythromycin A

35

Example 393

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-chlorobenzyl)-ureido)-methylene]-erythromycin A

40 Example 394

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((3,4-dichlorobenzyl)-ureido)-methylene]-erythromycin A

**Example 395**

**(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-fluorobenzyl)-ureido)-methylene]-erythromycin A**

5

**Example 396**

**(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-bromobenzyl)-ureido)-methylene]-erythromycin A**

10

**Example 397**

**(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-phenylethyl)-ureido)-methylene]-erythromycin A**

**Example 398**

15

**(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-thien-2-ylethyl)-ureido)-methylene]-erythromycin A**

Examples 329-398 were obtained starting from example 6 (5 mg) by following the same procedure as reported for Example 328.

20

The name and amount of starting material (i.e isocyanate) and LC/MS analysis (retention time and m/z) of examples 329-398 are reported in the table 4.

**Table 4**

Ex. N	Isocyanate	Amount (mg)	Ret. time (min)	Mass analysis m/z [MH] <sup>+</sup>
329	Isocyanatobenzene	1,78	5.50 6.10	746
330	2,6-Dichloro-4-isocyanatopyridine	2,83	6.51 7.16	815
331	4-Isocyanato-3,5-dimethylisoxazole	2,06	5.11	765
332	3-Isocyanatopyridine	1,80	5.00 5.43	747
333	2,2,4,4-Tetrafluoro-6-isocyanato-4H-1,3-benzodioxine	3,72	7.59 8.20	876

334	N-(4-isocyanatophenyl)- <i>N,N</i> -dimethylamine	2,42	5.90	789
335	1-Isocyanato-4-nitrobenzene	2,45	6.40 7.00	791
336	1-Isocyanato-3-nitrobenzene	2,45	6.33 6.87	791
337	1-Isocyanato-2-nitrobenzene	2,45	6.93	791
338	1-Isocyanato-3,5-dinitrobenzene	3,13	6.85 7.39	836
339	1-Isocyanato-4-methyl-2-nitrobenzene	2,66	6.81 7.57	805
340	1-Isocyanato-2-methyl-4-nitrobenzene	2,66	6.62 7.22	805
341	2-Isocyanato-1-methyl-4-nitrobenzene	2,66	6.47 6.90	805
342	4-Isocyanato-1-methyl-2-nitrobenzene	2,66	6.70 7.20	805
343	1-Isocyanato-2-methyl-3-nitrobenzene	2,66	6.40 6.80	805
344	2-Isocyanato-1-methyl-3-nitrobenzene	2,66	6.18 6.57	805
345	4-Chloro-2-isocyanato-1-nitrobenzene	2,97	7.11 7.83	825
346	2-Chloro-1-isocyanato-4-nitrobenzene	2,97	6.86 7.57	825
347	1-Chloro-4-isocyanato-2-nitrobenzene	2,97	6.91 7.51	825
348	4-Chloro-1-isocyanato-2-nitrobenzene	2,97	7.05 7.84	825
349	1-Fluoro-4-isocyanato-2-nitrobenzene	2,72	6.48 7.00	809

350	1-Fluoro-2-isocyanato-4-nitrobenzene	2,72	6.50 7.00	809
351	2-Isocyanato-1-methoxy-4-nitrobenzene	2,90	6.40 7.00	821
352	1-Isocyanato-2-methoxy-4-nitrobenzene	2,90	6.56 7.26	821
353	1-Isocyanato-4-methoxy-2-nitrobenzene	2,90	6.48 7.13	821
354	1-Isocyanato-4-methoxybenzene	2,23	5.60 5.90	776
355	1-Isocyanato-3-methoxybenzene	2,23	5.70 6.10	776
356	1-Isocyanato-2-methoxybenzene	2,23	5.40 6.10	776
357	4-Isocyanato-1,2-dimethoxybenzene	2,68	5.30 5.60	806
358	1-Isocyanato-2,4-dimethoxybenzene	2,68	5.60 6.10	806
359	2-Isocyanato-1,4-dimethoxybenzene	2,68	6.00 6.80	806
360	1-Isocyanato-3,5-dimethoxybenzene	2,68	6.17 6.64	806
361	2-Isocyanato-1,3-dimethoxybenzene	2,68	5.50 5.94	806
362	5-Isocyanato-1,3-benzodioxole	2,44	5.60 5.90	790
363	2-Isocyanato-1-methoxy-4-methylbenzene	2,44	5.90 6.60	790
364	1-Ethoxy-2-isocyanatobenzene	2,44	5.80 6.60	790
365	1-Ethoxy-4-isocyanatobenzene	2,44	5.80 6.10	790

366	1-Isocyanato-4-phenoxybenzene	3,16	7.03 7.30	838
367	1-Isocyanato-2-phenoxybenzene	3,16	6.70 7.30	838
368	1-Isocyanato-3-phenoxybenzene	3,16	7.10 7.40	838
369	2-(Cyclopentyloxy)-4-isocyanato-1-methoxybenzene	3,49	6.60 6.80	860
370	4-chloro-2-isocyanato-1-methoxybenzene	2,74	6.89 7.63	810
371	2-Chloro-4-isocyanato-1-methoxybenzene	2,74	6.10 6.40	810
372	1-Chloro-5-isocyanato-2,4-dimethoxybenzene	3,19	6.10 6.50	810
373	1-Isocyanato-4-(trifluoromethoxy)benzene	3,04	7.13 7.74	830
374	1-Isocyanato-2-(trifluoromethoxy)benzene	3,04	6.97 7.63	830
375	1-(Difluoromethoxy)-4-isocyanatobenzene	2,77	6.20 6.60	812
376	1-(Difluoromethoxy)-2-isocyanatobenzene	2,77	6.61 7.22	812
377	1-Isocyanato-4-(methylthio)benzene	2,47	6.20 6.50	792
378	1-Isocyanato-3-(methylthio)benzene	2,47	6.20 6.70	792
379	1-Isocyanato-2-(methylthio)benzene	2,47	5.90 6.50	792
380	1-Isocyanato-4-[(trifluoromethyl)thio]-benzene	3,28	7.60 8.20	846
381	1-(4-Isocyanatophenyl)ethanone	2,41	5.73 6.26	788



382	1-(3-Isocyanatophenyl)ethanone	2,41	5.83 6.34	788
383	4-Isocyanatobenzonitrile	2,15	6.05 6.59	771
384	3-Isocyanatobenzonitrile	2,15	6.10 6.60	771
385	1-Isocyanato-3-(trifluoromethyl)benzene	2,80	7.10 7.60	814
386	1-Chloro-4-isocyanatobenzene	2,30	6.70 7.30	780
387	1-Chloro-3-isocyanatobenzene	2,30	6.69 7.32	780
388	1-Chloro-2-isocyanatobenzene	2,30	6.69 7.32	780
389	1,2-Dichloro-4-isocyanatobenzene	2,81	7.23 7.92	814
390	1-Fluoro-4-isocyanatobenzene	2,05	5.80 6.20	764
391	(Isocyanatomethyl)benzene	1,99	6.00 6.40	760
392	1-(Isocyanatomethyl)-4-methoxybenzene	2,44	5.92 6.28	790
393	1-Chloro-2-(isocyanatomethyl)benzene	2,51	6.38 6.84	794
394	1,2-Dichloro-4-(isocyanatomethyl)benzene	3,02	6.99	828
395	1-Fluoro-4-(isocyanatomethyl)benzene	2,26	6.09 6.40	778
396	1-Bromo-4-(isocyanatomethyl)benzene	3,17	6.70 7.00	838
397	(2-Isocyanatoethyl)benzene	2,20	6.30 6.70	774

398	2-(2-Isocyanatoethyl)thiophene	2,29	6.10 6.50	780
-----	--------------------------------	------	--------------	-----

**Example 399****(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(benzoyl-thioureido)-methylene]-erythromycin A**

- 5 A solution of example 6 (0.005g) in MeOH (0.350mL) was reacted overnight at room temperature. After evaporating the solvent a solution of benzoyl isothiocyanate (2.4mg) in DCE (0.400mL) was added and the reaction mixture was heated at 60°C for 26h. After cooling to room temperature PS-Trisamine resin (loading 3.62mmol/g, 0.030g) was added and reacted at room temperature for 15h. The mixture was filtered and the resin rinsed with
- 10 DCE (2x0.230mL), DCM (3x0.160mL, 2x0.120mL). The filtrate was evaporated to give the title compound (0.003g).

LC/MS analysis (mobile phase: A/B from 90/10 to 10/90 in 16 min, 10/90 for 4 min; retention time: 9.1/10.0min, m/z ([MH]<sup>+</sup>) = 790.

- 15 Examples 400-425:

**Example 400****(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-(*N,N*-dimethylamino)-phenyl)-thioureido)-methylene]-erythromycin A**

20

**Example 401****(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-(*N,N*-diethylamino)phenyl)-thioureido)-methylene]-erythromycin A**

- 25 **Example 402**

**(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-(*N,N*-dimethylamino)-1-naphthyl)-thioureido)-methylene]-erythromycin A****Example 403**

- 30 **(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-nitrophenyl)-thioureido)-methylene]-erythromycin A**

**Example 404**

- 35 **(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-methyl-5-nitrophenyl)-thioureido)-methylene]-erythromycin A**

**Example 405****(11*S*,21*R*,*S*)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-chloro-4-nitrophenyl)-thioureido)-methylene]-erythromycin A**

**Example 406**

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-methoxy-4-nitrophenyl)-thioureido)-methylene]-erythromycin A

5

**Example 407**

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-methoxy-2-nitrophenyl)-thioureido)-methylene]-erythromycin A

10

**Example 408**

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-methoxyphenyl)-thioureido)-methylene]-erythromycin A

**Example 409**

15

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2,5-dimethoxyphenyl)-thioureido)-methylene]-erythromycin A

**Example 410**

20

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-methoxy-5-methylphenyl)-thioureido)-methylene]-erythromycin A

**Example 411**

25

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-methoxy-1,1'-biphenyl-3-yl)-thioureido)-methylene]-erythromycin A

**Example 412**

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-ethoxyphenyl)-thioureido)-methylene]-erythromycin A

30

**Example 413**

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-(benzyloxy)phenyl)-thioureido)-methylene]-erythromycin A

**Example 414**

35

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((5-chloro-2-methoxyphenyl)-thioureido)-methylene]-erythromycin A

**Example 415**

40

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-(methylthio)-phenyl)-thioureido)-methylene]-erythromycin A

**Example 416**

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-  
(benzyl)-thioureido)-methylene]-erythromycin A

Example 417

5 (11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-  
furylmethyl)-thioureido)-methylene]-erythromycin A

Example 418

10 (11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-  
methoxybenzyl)-thioureido)-methylene]-erythromycin A

Example 419

15 (11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-  
methoxybenzyl)-thioureido)-methylene]-erythromycin A

Example 420

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-  
chlorobenzyl)-thioureido)-methylene]-erythromycin A

20 Example 421

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((3,4-  
dichlorobenzyl)-thioureido)-methylene]-erythromycin A

Example 422

25 (11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-  
phenylethyl)-thioureido)-methylene]-erythromycin A

Example 423

30 (11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-  
morpholin-4-ylethyl)-thioureido)-methylene]-erythromycin A

Example 424

35 (11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-  
(3,4-dimethoxyphenyl)ethyl)-thioureido)-methylene]-erythromycin A

Example 425

(11S,21R,S)-3-Decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((2-(4-  
chlorophenyl)-ethyl)-thioureido)-methylene]-erythromycin A

40 Examples 400-425 were obtained starting from example 6 (5 mg) by following the same  
procedure as reported for Example 399.

The name and amount of starting material (i.e isocyanate) and LC/MS analysis (retention time) of examples **400-425** are reported in the table 5.

Table 5

5

Ex. N	Isothiocyanate	Amount (mg)	Ret. time (min)	Mass analysis m/z [MH] <sup>+</sup>
<b>400</b>	<i>N</i> -(4-Isothiocyanatophenyl)- <i>N,N</i> -dimethylamine	2,66	8.7 9.0	805
<b>401</b>	<i>N,N</i> -Diethyl- <i>N</i> -(4-isothiocyanatophenyl)amine	3,08	10.3	833
<b>402</b>	<i>N</i> -(4-Isothiocyanato-1-naphthyl)- <i>N,N</i> -dimethylamine	3,41	10.2 10.4	855
<b>403</b>	1-Isothiocyanato-4-nitrobenzene	2,69	9.5 10.2	807
<b>404</b>	2-Isothiocyanato-1-methyl-4-nitrobenzene	2,90	9.3 9.8	821
<b>405</b>	2-Chloro-1-isothiocyanato-4-nitrobenzene	3,21	9.9 10.5	841
<b>406</b>	1-Isothiocyanato-2-methoxy-4-nitrobenzene	3,14	9.7 10.5	837
<b>407</b>	1-Isothiocyanato-4-methoxy-2-nitrobenzene	3,14	9.3 9.8	837
<b>408</b>	1-Isothiocyanato-2-methoxybenzene	2,47	8.4 9.6	792
<b>409</b>	2-Isothiocyanato-1,4-dimethoxybenzene	2,92	8.5 9.6	822
<b>410</b>	2-Isothiocyanato-1-methoxy-4-methylbenzene	2,68	9.0	806
<b>411</b>	3-Isothiocyanato-4-methoxy-1,1'-biphenyl	3,61	10.4 11.3	868
<b>412</b>	1-Ethoxy-4-isothiocyanatobenzene	2,68	9.2 9.9	806

413	1-(Benzyloxy)-4-isothiocyanatobenzene	3,61	10.7 11.3	868
414	4-Chloro-2-isothiocyanato-1-methoxybenzene	2,98	9.4 10.5	826
415	1-Isothiocyanato-4-(methylthio)benzene	2,71	9.4 10.2	808
416	(Isothiocyanatomethyl)benzene	2,23	9.5	776
417	2-(Isothiocyanatomethyl)furan	2,08	8.5	765
418	1-(Isothiocyanatomethyl)-4-methoxybenzene	2,68	9.5	806
419	1-(Isothiocyanatomethyl)-2-methoxybenzene	2,68	9.6	806
420	1-Chloro-2-(isothiocyanatomethyl)benzene	2,75	10.2	810
421	1,2-Dichloro-4-(isothiocyanatomethyl)benzene	3,26	10.8 11.1	844
422	(2-Isothiocyanatoethyl)benzene	2,44	10.1	790
423	4-(2-Isothiocyanatoethyl)morpholine	2,58	6.6 6.9	799
424	4-(2-Isothiocyanatoethyl)-1,2-dimethoxybenzene	3,34	9.1	850
425	1-Chloro-4-(2-isothiocyanatoethyl)benzene	2,96	11.0	824

**Example 426****3-Amino-isonicotinamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-oxycarbonyl-(2-(amino)-ethylamino)-methylenel-erythromycin A**

- 5 To 3-amino-isonicotinic acid (0.001g) a solution of benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (0.004g) in anhydrous DMF (0.150mL) and a solution of DIPEA (0.003mL) in anhydrous DMF (0.150mL) were added followed by the addition of a solution of example 13 (0.005g) in anhydrous DMF (0.100mL). The reaction mixture was stirred at room temperature for 48h, then it was diluted with DCM (0.600mL), washed with a

5% NaHCO<sub>3</sub> aqueous solution (0.500mL), then passed through a phase-separation syringe. The aqueous phase was extracted with DCM (0.400mL) and the collected organic extracts evaporated under vacuum. The crude material was dissolved in DCM (0.500mL), loaded on a SCX-cartridge (250mg, loading 0.75mmol/g), washed with MeOH (4mL), then the product  
5 eluted with NH<sub>3</sub> (0.25M solution in MeOH, 1.5mL). After evaporating the solvent the title compound (0.003g) was obtained.

LC/MS analysis (mobile phase: A/B from 90/10 to 10/90 in 10 min, 10/90 for 2 min, mass range 150-1300 amu): retention time: 4.99 min, m/z ([MH]<sup>+</sup>) = 790.

10 Examples 427-601:

Example 427

5-Methyl-3-phenyl-isoxazole-4-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-  
15 erythromycin A

Example 428

1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-  
20 ethylamino)-methylene]-erythromycin A

Example 429

2-Trifluoromethyl-[1,8]naphthyridine-3-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-  
25 methylene]-erythromycin A

Example 430

6-Nitro-2-oxo-2*H*-chromene-3-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-  
30 erythromycin A

Example 431

4-Amino-2-methylsulfanyl-pyrimidine-5-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-  
35 methylene]-erythromycin A

Example 432

5-Chloro-1-methyl-1*H*-pyrazole-4-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-  
40 erythromycin A

Example 433

2-Pyrazin-2-yl-thiazole-4-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 434

- 5 3-Methyl-2-oxo-1,2-dihydro-quinoline-4-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 435

- 10 2-Methyl-imidazo[1,2,-*a*]pyridine-3-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 436

- 15 4-Methoxy-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 437

- 20 3-Methyl-5-(4-methyl-[1,2,3]thiadiazol-5-yl)-isoxazole-4-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 438

- 25 4-Acetyl-1-methyl-1*H*-pyrrole-2-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 439

- 30 6-[1,2,4]Triazol-1-yl-nicotinamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 440

- 35 Isonicotinamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 441

- 40 5-Oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 442



5-Nitro-1H-pyrazole-3-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 443

5 2-Methylsulfanyl-nicotinamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 444

10 7-Hydroxy-2-oxo-2H-chromene-3-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 445

15 Cinnoline-4-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 446

20 6-Amino-nicotinamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 447

25 1-Methyl-5-nitro-1H-pyrazole-4-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 448

30 4,7-Dimethyl-pyrazolo[5,1-c][1,2,4]triazine-3-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 449

2-Methoxy-nicotinamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

35 Example 450

3,5-Dimethyl-isoxazole-4-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 451

40 4-Oxo-4,5,6,7-tetrahydro-benzofuran-3-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

**Example 452**

**3-Amino-pyrazine-2-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A**

5

**Example 453**

**Pyrazine-2-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A**

10

**Example 454**

**4-Phenyl-[1,2,3]thiadiazole-5-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A**

15

**Example 455**

**5-Methyl-3-methylsulfanyl-isothiazole-4-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A**

20

**Example 456**

**2,6-Dimethyl-4-oxo-4*H*-pyran-3-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A**

25

**Example 457**

**1-Oxo-1,2-dihydro-isoquinoline-4-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A**

30

**Example 458**

**4-Acetyl-3-cyano-5-methyl-1*H*-pyrrole-2-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A**

35

**Example 459**

**4-Methyl-3-oxo-3,4-dihydro-2*H*-benzo[1,4]thiazine-6-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A**

40

**Example 460**

6-Methyl-imidazo[2,1-*b*]thiazole-5-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

5 Example 461

2-Phenoxy-nicotinamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 462

10 5-Nitro-1*H*-indole-2-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 463

15 4,8-Dihydroxy-quinoline-2-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 464

20 2-Hydroxy-quinoline-4-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 465

(1*H*-Indol-3-yl)-oxo-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

25 Example 466

Furan-2-yl-oxo-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 467

30 2-Amino-nicotinamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 468

35 1*H*-Benzotriazole-5-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 469

40 3-Methyl-furan-2-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 470

5-Chloro-1,3-dimethyl-1H-pyrazole-4-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

5 Example 471

4-Nitro-1H-pyrazole-3-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 472

10 4,6-Dimethyl-2-oxo-2H-pyran-5-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 473

15 2-Amino-5-chloropyrimidine-4-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 474

20 5-Methyl-1H-pyrazole-3-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 475

25 1-Methyl-5-oxopyrrolidine-3-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 476

30 2-Chloro-6-methyl-nicotinamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 477

35 (4R)-2-Thioxo-1,3-thiazolidine-4-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 478

40 2,2-Dimethyl-5-oxotetrahydrofuran-3-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 479

2,4-Dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

5 Example 480

2-(Methoxycarbonyl-nicotinamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 481

10 2-Methyl-1,8-naphthyridine-3-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 482

15 2-(Trifluoromethyl)-1,6-naphthyridine-3-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 483

20 1-Benzyl-5-oxopyrrolidine-3-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 484

25 3-(Aminocarbonyl)pyrazine-2-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 485

30 4-Amino-2-methylpyrimidine-5-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 486

35 Isoxazole-5-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 487

40 5-Methylisoxazole-3-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 488

6-Cyanonicotinamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 489

5 1-Ethyl-3-methyl-1*H*-pyrazole-5-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 490

10 5-Methylisoxazole-4-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 491

15 5-Oxo-1-(thien-2-ylmethyl)-pyrrolidine-3-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 492

20 2-(Pyridin-2-ylcarbonyl)-benzamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 493

25 1-(2-Furylmethyl)-5-oxopyrrolidine-3-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 494

30 5-(Methoxycarbonyl)-pyridine-2-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 495

35 2-(4-Methyl-1,2,3-thiadiazol-5-yl)-1,3-thiazole-4-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 496

40 3-Oxo-2,3-dihydro-1*H*-indazole-4-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 497

2-Methyl-1,6-naphthyridine-3-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

5 Example 498

4-Methyl-2-pyridin-4-yl-1,3-thiazole-5-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

10 Example 499

4-Methyl-2-pyridin-3-yl-1,3-thiazole-5-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

15 Example 500

4-(Morpholin-4-ylmethyl)-benzamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 501

20 6-(1*H*-Imidazol-1-yl)-nicotinamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 502

25 5-Methoxy-2-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-benzamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 503

30 4-Methyl-2-pyrazin-2-yl-1,3-thiazole-5-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 504

35 2,5-Dimethyl-1*H*-pyrrole-3-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 505

40 4-{[(4,6-Dimethylpyrimidin-2-yl)amino]carbonyl}-5-methylisoxazole-3-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 506

1-Methyl-1H-pyrazole-4-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 507

- 5 5-Chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 508

- 10 1-Pyrimidin-2-ylpiperidine-4-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 509

- 15 1-Methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 510

- 20 (4R)-2-Oxo-1,3-thiazolidine-4-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 511

- 25 (2S)-1-Acetylpyrrolidine-2-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 512

- 30 5-Nitro-furan-2-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 513

- 35 1-Methylpyrrolidine-2-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 514

- 40 4-Acetyl-3,5-dimethyl-1H-pyrrole-2-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 515



6-Methylnicotinamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 516

- 5 6-Methyl-3,4-dihydro-2*H*-pyran-5-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 517

- 10 2,7-Dimethylpyrazolo[1,5-*a*]pyrimidine-6-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 518

- 15 4-Methyl-1,2,3-thiadiazole-5-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 519

- 20 4-(Trifluoromethyl)-nicotinamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 520

- 25 4-Oxo-4*H*-chromene-2-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 521

- 30 5-Amino-1*H*-pyrazole-4-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 522

2-Chloronicotinamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 523

- 35 2-Oxo-2*H*-pyran-5-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 524

- 40 Furan-3-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 525

1,2,3-Thiadiazole-4-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

5 Example 526

1,5-Dimethyl-1H-pyrazole-3-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

10 Example 527

1H-Pyrazole-4-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 528

15 8-Methyl-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 529

20 2,6-Dimethoxynicotinamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 530

25 4-Chloro-1,3-dimethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 531

30 2-Methylnicotinamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 532

35 5-Amino-2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 533

40 4-Hydroxy-3-(morpholin-4-ylmethyl)-benzamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 534

5-Methylpyrazine-2-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 535

5 6-Oxo-1,4,5,6-tetrahydropyridazine-3-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 536

10 1*H*-pyrrole-2-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 537

15 2,2-Dimethyl-4-oxo-3,4-dihydro-2*H*-pyran-6-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 538

20 1-Methyl-1*H*-pyrrole-2-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 539

25 2,3-Dihydro-1,4-benzodioxine-2-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 540

30 2,4-Dimethyl-1,3-thiazole-5-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 541

35 1-Methyl-1,2,5,6-tetrahydropyridine-3-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 542

1-Oxy-pyridine-2-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 543

40 1-Acetylpiperidine-4-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

**Example 544**

Tetrahydrofuran-3-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

5

**Example 545**

(2*S*)-5-Oxopyrrolidine-2-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

10

**Example 546**

6-Hydroxynicotinamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

**Example 547**

15

3,6-Dichloropyridazine-4-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

**Example 548**

20

1-Ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

**Example 549**

25

Furan-2-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

**Example 550**

30

Pyridine-2-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

**Example 551**

Nicotinamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

35

**Example 552**

Tetrahydrofuran-2-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

**Example 553**

40

2-Methyl-furan-3-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 554

(2R)-Tetrahydrofuran-2-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

5 Example 555

2-(5-Oxopyrrolidin-2-ylsulfanyl)-benzamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

10 Example 556

1-Allyl-2-oxo-1,2-dihydropyridine-3-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

15 Example 557

2-Methyl-4-(trifluoromethyl)-1,3-thiazole-5-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

20 Example 558

6-Hydroxy-1-methyl-2-oxo-1,2-dihydropyrimidine-4-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

25 Example 559

3-Methylisoxazole-4-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 560

30 5-Methoxy-1,3-oxazole-2-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 561

35 2-[6-(Acetylamino)-pyridin-3-ylsulfanyl]-nicotinamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 562

40 4-(4-Methylpiperazin-1-yl)-3-nitro-benzamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 563

4-Isopropyl-1,2,3-thiadiazole-5-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 564

3-Oxo-2-phenyl-2,3-dihydropyridazine-4-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 565

5-Bromo-2-oxo-1,2-dihydropyridine-3-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 566

1-(Methoxycarbonyl)piperidine-4-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 567

1-(6-Chloropyridazin-3-yl)piperidine-4-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 568

4-Chloro-6-oxo-1-phenyl-1,6-dihydropyridazine-3-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 569

1-(3-Chlorophenyl)-4-methoxy-6-oxo-1,6-dihydropyridazine-3-carboxamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 570

(1-Methyl-4-nitro-1*H*-pyrazol-5-yl)-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 571

(1,3-Dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)-acetamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

5 Example 572

5-Oxo-4,5-dihydrofuran-3-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 573

10 2R,4S)-4-(Acetyloxy)-1,3-oxathiolane-2-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 574

15 3-Hydroxyisonicotinamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 575

20 3-Hydroxypyridine-2-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 576

25 2-Hydroxynicotinamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 577

30 7-Hydroxy-4-oxo-4H-chromene-2-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 578

1-Oxy-nicotinamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

35 Example 579

1H-Indole-2-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 580

40 5-Methoxy-1H-indole-2-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 581

6-chloro-4-oxo-4H-chromene-2-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

5

Example 582

Quinoline-2-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

10

Example 583

4-Hydroxy-6-methoxyquinoline-2-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

15

Example 584

4-Methyl-3-oxo-3,4-dihydroquinoxaline-2-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

20

Example 585

4-(2-Hydroxyethyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

25

Example 586

3-Methoxyquinoxaline-2-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

30

Example 587

1-Benzofuran-2-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

35

Example 588

6-Ethyl-5-oxothiophomorpholine-3-carboxamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

40

Example 589

2-Chloro-1-oxy-nicotinamide of (11S,21R,S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 590



Oxo-(thien-2-yl)-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 591

5 Oxo-(phenyl)-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 592

10 3-(2-Nitrophenyl)-2-oxo-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 593

15 3-(1*H*-Indol-3-yl)-2-oxo-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 594

2-Oxo-3-phenyl-propionamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

20 Example 595

(2*E*)-3-(1*H*-Imidazol-4-yl)-acrylamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 596

25 (2*E*)-3-(1*H*-Indol-3-yl)-acrylamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 597

30 3-(1,3-Benzodioxol-5-yl)prop-2-ynamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 598

(2*E*)-3-Quinolin-3-yl-acrylamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

35

Example 599

(2*E*)-3-Quinolin-2-yl-acrylamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

40

Example 600

(Quinoxalin-2-ylsulfany)-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

**Example 601**

[5-(5-Nitro-furan-2-yl)-[1,3,4]oxadiazol-2-ylsulfanyl]-acetamide of (11*S*,21*R*,*S*)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(amino)-ethylamino)-methylene]-erythromycin A

Example 427-601 were obtained starting from example 13 (5 mg) by following the same procedure as reported for Example 426.

The name and amount of starting material (i.e carboxylic acid) and LC/MS analysis (retention time and m/z) of examples 427-601 are reported in table 6.

**Table 6**

Ex. N	Carboxylic acid	Amount (mg)	Ret. time (min)	Mass analysis m/z [MH] <sup>+</sup>
427	5-Methyl-3-phenyl-isoxazole-4-carboxylic acid	1,5	6,75	855
428	1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1 <i>H</i> -pyrazole-4-carboxylic acid	1,7	5,7	884
429	2-Trifluoromethyl-[1,8]naphthyridine-3-carboxylic acid	1,8	5,82	894
430	6-Nitro-2-oxo-2 <i>H</i> -chromene-3-carboxylic acid	1,8	6,88	887
431	4-Amino-2-methylsulfanyl-pyrimidine-5-carboxylic acid	1,4	5,94	837
432	5-Chloro-1-methyl-1 <i>H</i> -pyrazole-4-carboxylic acid	1,2	5,47	812
433	2-Pyrazin-2-yl-thiazole-4-carboxylic acid	1,5	5,92	859
434	3-Methyl-2-oxo-1,2-dihydro-quinoline-4-carboxylic acid	1,5	5,45	855

435	2-Methyl-imidazo[1,2- <i>a</i> ]pyridine-3-carboxylic acid	1,3	5,64	828
436	4-Methoxy-1,3-dimethyl-1 <i>H</i> -pyrazolo[3,4- <i>b</i> ]pyridine-5-carboxylic acid	1,7	5,7	873
437	3-Methyl-5-(4-methyl-[1,2,3]thiadiazol-5-yl)-isoxazole-4-carboxylic acid	1,7	6,68	877
438	4-Acetyl-1-methyl-1 <i>H</i> -pyrrole-2-carboxylic acid	1,2	5,56	819
439	6-[1,2,4]Triazol-1-yl-nicotinic acid	1,4	5,52	842
440	Isonicotinic acid	0,9	5,22	775
441	5-Oxo-2,3-dihydro-5 <i>H</i> -thiazolo[3,2- <i>a</i> ]pyrimidine-6-carboxylic acid	1,5	5,35	850
442	5-Nitro-1 <i>H</i> -pyrazole-3-carboxylic acid	1,2	5,44	809
443	2-Methylsulfanyl-nicotinic acid	1,3	6,07	821
444	7-Hydroxy-2-oxo-2 <i>H</i> -chromene-3-carboxylic acid	1,5	5,7	856
445	Cinnoline-4-carboxylic acid	1,3	5,7	826
446	6-Amino-nicotinic acid	1,0	5,1	790
447	1-Methyl-5-nitro-1 <i>H</i> -pyrazole-4-carboxylic acid	1,3	6	823

448	4,7-Dimethyl-pyrazolo[5,1- c][1,2,4]triazine-3-carboxylic acid	1,4	6,4	844
449	2-Methoxy-nicotinic acid	1,1	6,2	805
450	3,5-Dimethyl-isoxazole-4-carboxylic acid	1,1	6	793
451	4-Oxo-4,5,6,7-tetrahydro-benzofuran-3- carboxylic acid	1,3	6,2	832
452	3-Amino-pyrazine-2-carboxylic acid	1,0	5,9	791
453	Pyrazine-2-carboxylic acid	0,9	5,6	776
454	4-Phenyl-[1,2,3]thiadiazole-5- carboxylic acid	1,5	7,1	858
455	5-Methyl-3-methylsulfanyl-isothiazole- 4-carboxylic acid	1,4	6,7	841
456	2,6-Dimethyl-4-oxo-4H-pyran-3- carboxylic acid	1,3	5,5	820
457	1-Oxo-1,2-dihydro-isoquinoline-4- carboxylic acid	1,4	5,5	841
458	4-Acetyl-3-cyano-5-methyl-1H-pyrrole- 2-carboxylic acid	1,4	5,8	844
459	4-Methyl-3-oxo-3,4-dihydro-2H- benzo[1,4]thiazine-6-carboxylic acid	1,7	6,2	875
460	6-Methyl-imidazo[2,1-b]thiazole-5- carboxylic acid	1,4	5,8	834

461	2-Phenoxy-nicotinic acid	1,6	6,9	867
462	5-Nitro-1 <i>H</i> -indole-2-carboxylic acid	1,5	6,9	858
463	4,8-Dihydroxy-quinoline-2-carboxylic acid	1,5	5,6	857
464	2-Hydroxy-quinoline-4-carboxylic acid	1,4	5,5	841
465	(1 <i>H</i> -Indol-3-yl)-oxo-acetic acid	1,4	6,7	841
466	Furan-2-yl-oxo-acetic acid	1,0	6,3	792
467	2-Amino-nicotinic acid	1,0	9.1	790
468	1 <i>H</i> -Benzotriazole-5-carboxylic acid	1.2	6.9	815
469	3-Methyl-furan-2-carboxylic acid	1.0	11	778
470	5-Chloro-1,3-dimethyl-1 <i>H</i> -pyrazole-4-carboxylic acid	1.3	5.7	826
471	4-Nitro-1 <i>H</i> -pyrazole-3-carboxylic acid	1,2	5,40	809
472	4,6-Dimethyl-2-oxo-2 <i>H</i> -pyran-5-carboxylic acid	1,3	5,48 5,89	820
473	2-Amino-5-chloropyrimidine-4-carboxylic acid	1,3	5,49	825

474	5-Methyl-1 <i>H</i> -pyrazole-3-carboxylic acid	0,9	5,16	778
475	1-Methyl-5-oxopyrrolidine-3-carboxylic acid	1,1	4,67	795
476	2-Chloro-6-methylnicotinic acid	1,3	5,75	823
477	(4 <i>R</i> )-2-Thioxo-1,3-thiazolidine-4-carboxylic acid	1,2	5,72	815
478	2,2-Dimethyl-5-oxotetrahydrofuran-3-carboxylic acid	1,2	5,66	810
479	2,4-Dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid	1,3	4,70	808
480	2-(Methoxycarbonyl-nicotinic acid	1,4	5,79	833
481	2-Methyl-1,8-naphthyridine-3-carboxylic acid	1,4	5,05	840
482	2-(Trifluoromethyl)-1,6-naphthyridine-3-carboxylic acid	1,8	6,15	894
483	1-Benzyl-5-oxopyrrolidine-3-carboxylic acid	1,6	5,93	871
484	3-(Aminocarbonyl)pyrazine-2-carboxylic acid	1,2	4,66	819
485	4-Amino-2-methylpyrimidine-5-carboxylic acid	1,1	4,98	805
486	Isoxazole-5-carboxylic acid	0,8	4,46 5,55	765

487	5-Methylisoxazole-3-carboxylic acid	0,9	5,98	779
488	6-Cyanonicotinic acid	1,1	5,90	800
489	1-Ethyl-3-methyl-1 <i>H</i> -pyrazole-5-carboxylic acid	1,2	6,05	806
490	5-Methylisoxazole-4-carboxylic acid	0,9	4,35	779
491	5-Oxo-1-(thien-2-ylmethyl)-pyrrolidine-3-carboxylic acid	1,7	5,79	877
492	2-(Pyridin-2-ylcarbonyl)-benzoic acid	1,7	6,18 6,44	879
493	1-(2-Furylmethyl)-5-oxopyrrolidine-3-carboxylic acid	1,6	5,55	861
494	5-(Methoxycarbonyl)-pyridine-2-carboxylic acid	1,4	6,24	833
495	2-(4-Methyl-1,2,3-thiadiazol-5-yl)-1,3-thiazole-4-carboxylic acid	1,7	6,35	879
496	3-Oxo-2,3-dihydro-1 <i>H</i> -indazole-4-carboxylic acid	1,3	5,63	830
497	2-Methyl-1,6-naphthyridine-3-carboxylic acid	1,4	5,19	840
498	4-Methyl-2-pyridin-4-yl-1,3-thiazole-5-carboxylic acid	1,6	5,94	872
499	4-Methyl-2-pyridin-3-yl-1,3-thiazole-5-carboxylic acid	1,6	5,94	872

500	4-(morpholin-4-ylmethyl)-benzoic acid hydrochloride	1,9	5,68	873
501	6-(1 <i>H</i> -Imidazol-1-yl)-nicotinic acid	1,4	5,40	841
502	5-Methoxy-2-(1,3,5-trimethyl-1 <i>H</i> -pyrazol-4-yl)-benzoic acid	1,9	6,13	912
503	4-Methyl-2-pyrazin-2-yl-1,3-thiazole-5-carboxylic acid	1,7	6,18	873
504	2,5-Dimethyl-1 <i>H</i> -pyrrole-3-carboxylic acid	1,0	5,64	791
505	4-[[[(4,6-Dimethylpyrimidin-2-yl)amino]carbonyl]-5-methylisoxazole-3-carboxylic acid	2,1	6,49	928
506	1-Methyl-1 <i>H</i> -pyrazole-4-carboxylic acid	0,9	5,03	778
507	5-Chloro-1-methyl-3-(trifluoromethyl)-1 <i>H</i> -pyrazole-4-carboxylic acid	1,7	6,57	880
508	1-Pyrimidin-2-ylpiperidine-4-carboxylic acid	1,5	5,89	859
509	1-Methyl-3-(trifluoromethyl)-1 <i>H</i> -pyrazole-4-carboxylic acid	1,4	6,02	846
510	(4 <i>R</i> )-2-Oxo-1,3-thiazolidine-4-carboxylic acid	1,1	5,11	799
511	(2 <i>S</i> )-1-Acetylpyrrolidine-2-carboxylic acid	1,2	4,95	809
512	5-Nitro-furan-2-carboxylic acid	1,2	6,18	809



513	1-Methylpyrrolidine-2-carboxylic acid	1,1	5,28	781
514	4-Acetyl-3,5-dimethyl-1 <i>H</i> -pyrrole-2-carboxylic acid	1,4	5,63	833
515	6-Methylnicotinic acid	1,0	5,31	789
516	6-Methyl-3,4-dihydro-2 <i>H</i> -pyran-5-carboxylic acid	1,1	5,95	794
517	2,7-Dimethylpyrazolo[1,5- <i>a</i> ]pyrimidine-6-carboxylic acid	1,4	5,63	843
518	4-Methyl-1,2,3-thiadiazole-5-carboxylic acid	1,1	6,01	796
519	4-(Trifluoromethyl)-nicotinic acid	1,4	5,98	843
520	4-Oxo-4 <i>H</i> -chromene-2-carboxylic acid	1,4	6,2	842
521	5-Amino-1 <i>H</i> -pyrazole-4-carboxylic acid	0,9	5,1	779
522	2-Chloronicotinic acid	1,2	5,7	809
523	2-Oxo-2 <i>H</i> -pyran-5-carboxylic acid	1,0	5,4 5,8	792
524	Furan-3-carboxylic acid	0,8	5,9	764
525	1,2,3-Thiadiazole-4-carboxylic acid	1,0	5,8	782

526	1,5-Dimethyl-1 <i>H</i> -pyrazole-3-carboxylic acid	1,0	5,6	792
527	1 <i>H</i> -Pyrazole-4-carboxylic acid	0,8	4,5	764
528	8-Methyl-4-oxo-4 <i>H</i> -pyrido[1,2- <i>a</i> ]pyrimidine-3-carboxylic acid	1,5	5,7	856
529	2,6-Dimethoxynicotinic acid	1,4	6,9	835
530	4-Chloro-1,3-dimethyl-1 <i>H</i> -pyrazolo[3,4- <i>b</i> ]pyridine-5-carboxylic acid	1,7	6,2	877
531	2-Methylnicotinic acid	1,0	5,4	781
532	5-Amino-2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid	1,3	4,8	823
533	4-Hydroxy-3-(morpholin-4-ylmethyl)-benzoic acid	1,9	6,0	889
534	5-Methylpyrazine-2-carboxylic acid	1,0	5,8	790
535	6-Oxo-1,4,5,6-tetrahydropyridazine-3-carboxylic acid	1,1	5,1	794
536	1 <i>H</i> -pyrrole-2-carboxylic acid	0,8	5,9	763
537	2,2-Dimethyl-4-oxo-3,4-dihydro-2 <i>H</i> -pyran-6-carboxylic acid	1,3	6,0	822
538	1-Methyl-1 <i>H</i> -pyrrole-2-carboxylic acid	0,9	6,3	777

539	2,3-Dihydro-1,4-benzodioxine-2-carboxylic acid	1,3	6,9	832
540	2,4-Dimethyl-1,3-thiazole-5-carboxylic acid	1,2	5,8	809
541	1-Methyl-1,2,5,6-tetrahydropyridine-3-carboxylic acid	1,3	4,9	793
542	1-Oxy-pyridine-2-carboxylic acid	1,0	5,3	791
543	1-Acetylpiperidine-4-carboxylic acid	1,3	5,1	823
544	Tetrahydrofuran-3-carboxylic acid	0,9	5,6	768
545	(2S)-5-Oxopyrrolidine-2-carboxylic acid	1,0	4,7	781
546	6-Hydroxynicotinic acid	1,0	4,6/4,8	791
547	3,6-Dichloropyridazine-4-carboxylic acid	1,4	6,4	844
548	1-Ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid	1,7	6,7	884
549	Furan-2-carboxylic acid	0,8	5,8	764
550	Pyridine-2-carboxylic acid	0,9	6,0	775
551	Nicotinic acid	0,9	5,3	775

552	Tetrahydrofuran-2-carboxylic acid	0,9	5,6	768
553	2-Methyl-furan-3-carboxylic acid	0,9	6,3	778
554	(2R)-Tetrahydrofuran-2-carboxylic acid	0,9	5,6	768
555	2-(5-Oxopyrrolidin-2-ylsulfanyl)-benzoic acid	1,8	5,7 6,1	889
556	1-Allyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid	1,3	6,0	831
557	2-Methyl-4-(trifluoromethyl)-1,3-thiazole-5-carboxylic acid	1,6	6,7	863
558	6-Hydroxy-1-methyl-2-oxo-1,2-dihydropyrimidine-4-carboxylic acid	1,3	5,1	822
559	3-Methylisoxazole-4-carboxylic acid	0,9	5,9	779
560	5-Methoxy-1,3-oxazole-2-carboxylic acid	1,1	5,4 5,8	795
561	2-[6-(Acetylamino)-pyridin-3-ylsulfanyl]-nicotinic acid	2,2	5,9	941
562	4-(4-Methylpiperazin-1-yl)-3-nitro-benzoic acid	2,0	6,0	917
563	4-Isopropyl-1,2,3-thiadiazole-5-carboxylic acid	1,3	6,9	824
564	3-Oxo-2-phenyl-2,3-dihydropyridazine-4-carboxylic acid	1,6	6,7	868

565	5-Bromo-2-oxo-1,2-dihydropyridine-3-carboxylic acid	1,6	5,6	869
566	1-(Methoxycarbonyl)piperidine-4-carboxylic acid	1,4	5,6	839
567	1-(6-Chloropyridazin-3-yl)piperidine-4-carboxylic acid	1,8	6,0	893
568	4-Chloro-6-oxo-1-phenyl-1,6-dihydropyridazine-3-carboxylic acid	1,9	6,2 6,6	902
569	1-(3-Chlorophenyl)-4-methoxy-6-oxo-1,6-dihydropyridazine-3-carboxylic acid	2,1	6,2 6,5	932
570	(1-Methyl-4-nitro-1 <i>H</i> -pyrazol-5-yl)-acetic acid	1,4	5,9	837
571	(1,3-Dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1 <i>H</i> -purin-8-yl)-acetic acid	1,8	5,2	890
572	5-Oxo-4,5-dihydrofuran-3-carboxylic acid	1,0	7,2	780
573	(2 <i>R</i> ,4 <i>S</i> )-4-(Acetyloxy)-1,3-oxathiolane-2-carboxylic acid	1,4	6,0	844
574	3-Hydroxyisonicotinic acid	1,0	5,2	791
575	3-Hydroxypyridine-2-carboxylic acid	1,0	6,7 7,1	791
576	2-Hydroxynicotinic acid	1,0	5,0	791
577	7-Hydroxy-4-oxo-4 <i>H</i> -chromene-2-carboxylic acid	1,5	5,4	858

578	1-Oxy-nicotinic acid	1,0	4,8	791
579	1 <i>H</i> -Indole-2-carboxylic acid	1,2	6,8	813
580	5-Methoxy-1 <i>H</i> -indole-2-carboxylic acid	1,4	6,7	843
581	6-chloro-4-oxo-4 <i>H</i> -chromene-2-carboxylic acid	1,7	7,0	876
582	Quinoline-2-carboxylic acid	1,3	7,1	825
583	4-Hydroxy-6-methoxyquinoline-2-carboxylic acid	1,6	5,7	871
584	4-Methyl-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid	1,5	5,8	856
585	4-(2-Hydroxyethyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid	1,7	5,3	886
586	3-Methoxyquinoxaline-2-carboxylic acid	1,5	6,6	856
587	1-Benzofuran-2-carboxylic acid	1,2	6,8	814
588	6-Ethyl-5-oxothiomorpholine-3-carboxylic acid	1,4	5,8	841
589	2-Chloro-1-oxy-nicotinic acid	1,3	4,5	825
590	Oxo(thien-2-yl)-acetic acid	1,2	6,9	808

591	Oxo-(phenyl)-acetic acid	1,1	6,9	802
592	3-(2-Nitrophenyl)-2-oxo-propionic acid	1,6	6,7 7,1	861
593	3-(1 <i>H</i> -Indol-3-yl)-2-oxo-propionic acid	1,5	8,1	855
594	2-Oxo-3-phenyl-propionic acid	1,2	6,7 7,3	816
595	(2E)-3-(1 <i>H</i> -Imidazol-4-yl)-acrylic acid	1,0	4,9	790
596	(2E)-3-(1 <i>H</i> -Indol-3-yl)-acrylic acid	1,4	6,4 6,7	839
597	3-(1,3-Benzodioxol-5-yl)prop-2-ynoic acid	1,4	6,8	842
598	(2E)-3-Quinolin-3-yl-acrylic acid	1,5	6,2	851
599	(2E)-3-Quinolin-2-yl-acrylic acid	1,5	6,2	851
600	(Quinoxalin-2-ylsulfanyl)-acetic acid	1,6	6,7	872
601	[5-(5-Nitro-furan-2-yl)- [1,3,4]oxadiazol-2-ylsulfanyl]-acetic acid	2,0	6,3 6,7	923

**Pharmacy examples****Tablets**

		mg/tab
5	Active ingredient	320
	Lactose	150
	Ethyl cellulose	20
	Sodium lauryl sulphate	7
10	Magnesium stearate	3
	Tablet core	500

The active ingredient and the lactose are blended together and then granulated using water as granulating fluid. The dried granules are blended with ethyl cellulose, sodium lauryl sulphate and magnesium stearate and the tablet core formed using an appropriate punch. The tablet may be coated using conventional technique and coatings.

**Injection**

The sterile vials were filled with the sterile active ingredient (500 mg). Purge the vial head space with sterile nitrogen; close the vials using rubber and metal overseals. The product may be constituted by dissolving in water for injection (10 ml) or other suitable sterile vehicle for injection shortly before administration.

**Activity data**

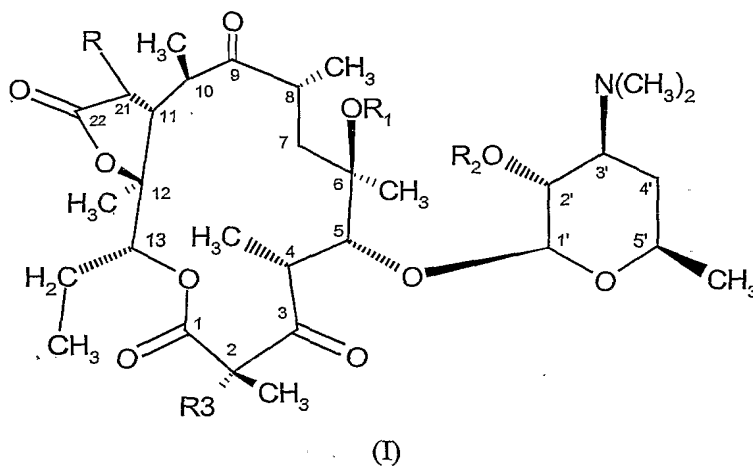
The value of MIC (microbial inhibition concentration), obtained according to NCCLS (National Committee for Clinical Laboratory Standards), of the preferred compounds of the invention against erythromycin susceptible *Streptococcus pneumoniae* and *Streptococcus pyogenes* are less than or equal to 1 µg/ml.

In particular Examples 70, 56, 54, 49, 51, 58, 75, 66, 47, 52, 117 showed MIC ≤ 0.1 µg/ml against erythromycin susceptible *Streptococcus pneumoniae* strains. Furthermore Examples 70, 56, 54, 49, 51, 58, 75, 66, 47, 52, 117 showed MIC in the range ≤ 8 - 0.06 µg/ml against erythromycin resistant *Streptococcus pneumoniae* strains.



Claims

1. A compound of formula (I)



wherein

R is hydrogen, cyano,  $(\text{CH}_2)_n\text{A-X-R}_4$  or  $(\text{CH}_2)_n\text{R}_5$ ;

A is a group selected from  $-\text{N}(\text{R}_6)-$ ,  $-\text{N}[\text{C}(\text{O})\text{R}_6]-$ ,  $-\text{N}(\text{R}_6)\text{C}(\text{O})-$ ,  $-\text{N}(\text{R}_6)\text{S}(\text{O})_2-$ ,  $-\text{N}(\text{R}_6)\text{C}(\text{O})\text{O}-$ ,  $-\text{N}=\text{C}(\text{R}_6)-$  or  $-\text{N}(\text{R}_6)\text{C}(\text{Y})\text{N}(\text{R}_7)-$ ;

$\text{R}_1$  is  $\text{C}_{1-6}$  alkyl or  $\text{C}_{3-6}$  alkenyl;

$\text{R}_2$  is hydrogen or a hydroxyl protecting group;

$\text{R}_3$  is hydrogen or halogen;

X is a bond, a  $\text{C}_{1-10}$  alkylene, a  $\text{C}_{2-10}$  alkenylene or a  $\text{C}_{2-10}$  alkynylene chain wherein said chains are:

i) optionally interrupted by a bivalent radical group selected from  $-\text{O}-$ ,  $-\text{N}(\text{R}_8)-$ ,  $-\text{C}(\text{O})-$ ,  $-\text{N}(\text{R}_8)\text{C}(\text{Y})\text{N}(\text{R}_9)-$ ,  $-\text{S}(\text{O})\text{m}-$ ,  $-\text{N}(\text{R}_8)\text{C}(\text{O})-$ ,  $-\text{C}(\text{O})\text{N}(\text{R}_8)-$ ,  $-\text{N}(\text{R}_8)\text{C}(\text{O})\text{C}(\text{O})-$ ,  $-\text{C}(\text{O})\text{O}-$  or  $-\text{C}(\text{NOR}_6)-$  and/or

ii) optionally substituted by one or two groups selected from:

$\text{C}_{1-4}$  alkyl, oxo,  $\text{C}_{1-4}$  alkoxy, halogen, cyano, phenoxy, hydroxy,  $\text{NR}_8\text{R}_9$ ,  $\text{N}(\text{R}_8)\text{C}(\text{O})\text{R}_9$ ,  $=\text{NOR}_6$ ,  $\text{NR}_8\text{C}(\text{Y})\text{NR}_9$  or optionally substituted phenyl;

$\text{R}_4$  is selected from:

hydrogen,

optionally substituted phenyl,

optionally substituted  $\text{C}_{3-7}$  cycloalkyl,

optionally substituted 9 to 10 membered fused bicyclic carbocyclic,

optionally substituted 5 or 6 membered heteroaryl in which the 5-membered heteroaryl contains at least one heteroatom selected from oxygen, sulphur or nitrogen and the 6-membered heteroaryl group contains from 1 to 3 nitrogen atoms,

optionally substituted 5-6 membered heterocyclic,

or

$\text{R}_4$  is an optionally substituted 9 or 10 membered fused bicyclic heterocyclic having at least one heteroatom selected from oxygen, sulphur or nitrogen;

R<sub>5</sub> is a 5 or 6 membered heterocyclic containing at least one nitrogen, optionally substituted by one or two groups selected from oxo or 9 or 10 membered fused bicyclic heterocyclic having at least one heteroatom selected from oxygen, sulphur or nitrogen;

R<sub>6</sub> and R<sub>7</sub> are independently hydrogen, C<sub>1-4</sub> alkyl or phenyl which is optionally substituted by one or two C<sub>1-4</sub> alkyl groups;

R<sub>8</sub> and R<sub>9</sub> are independently hydrogen, phenyl (which may be substituted by one or two C<sub>1-4</sub> alkyl) or R<sub>8</sub> and R<sub>9</sub> are independently C<sub>1-4</sub> alkyl which is optionally substituted by 1 or 2 groups selected from:

- phenyl, C<sub>1-4</sub> alkoxy,
- cyano,
- 5-membered heteroaryl containing 1 or 2 heteroatoms selected from oxygen, sulphur or nitrogen or the 6-membered heteroaryl group contains from 1 to 3 nitrogen atoms,
- hydroxy,
- oxo,
- carboxy;

Y is an oxygen or a sulphur atom;

n is 0 or an integer from 1 to 3;

m is 0, 1 or 2;

and pharmaceutically acceptable salts and solvates thereof.

20

2. A compound as claimed in claim 1 wherein R is (CH<sub>2</sub>)<sub>n</sub>A-X-R<sub>4</sub> or (CH<sub>2</sub>)<sub>n</sub>R<sub>5</sub>.

25

3. A compound as claimed in claim 1 or 2 wherein R<sub>1</sub> is methyl or 2-propenyl.

4. A compound as claimed in any claims 1 to 3 wherein R<sub>2</sub> is hydrogen.

30

5. A compound as claimed in any claims 1 to 4 wherein R<sub>3</sub> is hydrogen or fluorine.

6. A compound as claimed in any claims 1 to 5 wherein A is selected from -NH-, -NHC(O)- or -NHC(Y)NH-.

35

7. A compound as claimed in any claims 1 to 6 wherein X is a C<sub>1-4</sub> alkylene chain which is optionally interrupted by a bivalent radical selected from -O-, -NH-, -C(O)-, -NHC(O)-, -S(O)<sub>2</sub>- -S- and /or such a C<sub>1-4</sub> alkylene chain is optionally substituted by one group selected from NH<sub>2</sub>, C<sub>1-4</sub> alkyl, oxo or N-OH.

40

8. A compound as claimed in any claims 1 to 7 wherein R<sub>4</sub> is phenyl (optionally substituted by 1 to 3 groups which may be the same or different selected from nitro, amino, methyl, C<sub>1-4</sub> alkoxy ie methoxy or hydroxy), 1-imidazolyl (optionally substituted by 1 to 3 groups which may be the same or different selected from pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, phenyl, m-nitrophenyl, dichlorophenyl, C<sub>1-4</sub> alkyl i.e methyl,

trifluoromethylphenyl, thiophen-2-yl, thiazol-2-yl), 3-trifluoromethylpyrazol-4-yl, 1-pyrazolyl (optionally substituted by 1 to 3 groups which may be the same or different selected from alogen (i.e. chlorine, fluorine), pyridin-2-yl, pyridin-4-yl, quinolin-2-yl, quinolin-4-yl, quinoxalin-2-yl, pyrimidin-4-yl, C<sub>1-4</sub> alkyl i.e methyl, 1,3 benzooxazol-2-yl, , p-chloro phenyl, difluoro phenyl, pyrazin-2-yl thiazol-5-yl,) 1H-indol-3-yl, 1H-indol-2-yl, 3-methoxy-quinoxalin-2-yl, 2-quinolinyl 3-quinolinyl, 4-quinolinyl, 4-pyridinyl, 3-pyridinyl (optionally substituted by one amino), 5methyl furan-2-yl, 3-thiophenyl, 6-methoxy-7H-purin-7-yl, quinoxalin-2-yl, 3-methoxy quinoxalin-2-yl 6-methoxy-2-oxo-1, 3-benzoxazol-3(2H)-yl, 1H-pyrrolo[2,3-b]pyridin-1-yl, 2-(methylthio)-1H-benzimidazol-1-yl, 1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl, 6-methoxy-2-oxo-1,3-benzoxazol-3(2H)-yl, 3H-imidazo[4,5-b]pyridin-3-yl, 1,3-benzoxazol-2-yl, benzothiazol-2-yl, 1,3 benzo[1,3]dioxolyl, 3-(5-cyano-3,4-dimethylthien-2-yl)-1H-1,2,4-triazol-1-yl, 2,3-dihydro-benzo[1,4]dioxin-6-yl, 2,4-dimethyl-1,3-thiazol-5-yl or 4-oxo-4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl.

9. A compound as claimed in any claims 1 to 8 wherein R<sub>1</sub> is methyl, R<sub>2</sub> or R<sub>3</sub> is hydrogen, A is -NH-, -NHC(O)-, X is C<sub>1-4</sub> alkylene chain which is optionally interrupted by a bivalent radical selected from -O-, -NH-, -C(O)-, -NHC(O)-, -S(O)<sub>2</sub>- -S- and /or such a C<sub>1-4</sub> alkylene chain is optionally substituted by one group selected from NH<sub>2</sub>, C<sub>1-4</sub> alkyl, oxo or N-OH, R<sub>4</sub> is a group selected from 4-(pyridin-3-yl)-imidazol-1-yl, 4-(pyridin-3-yl)-imidazol-1-yl, quinoxalin-2-yl, quinoxalin-2-yl, quinolin-4-yl, quinoxalin-2-yl, -(2,3-dihydro-benzo[1,4]dioxin-6-yl, 4-oxo-4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl, 4-methoxy-3-nitrophenyl, 2-hydroxy-4,5-dimethoxy-phenyl, 3-hydroxy-4-methoxy-phenyl, 3,4-dimethoxy-phenyl, 4-hydroxy-3-methoxy-phenyl, 3-methoxy-quinoxalin-2-yl, 3-amino-4-methoxy-phenyl, 4-(pyridin-3-yl)-imidazol-1-yl, quinolin-4-yl, 4-pyrimidin-4-yl-pyrazol-1-yl, 2-(methylthio)-1H-benzimidazol-1-yl, -[3-(4-chlorophenyl)-1H-pyrazol-5-yl]propylamino)-methylene], 6-methoxy-2-oxo-1,3-benzoxazol-3(2H)-yl, 1H-pyrrolo[2,3-b]pyridin-1-yl, 3-(2,4-dimethyl-1,3-thiazol-5-yl)-1H-pyrazol-1-yl, 4-phenyl-1H-imidazol-1-yl, 4-pyridin-4-yl-1H-imidazol-1-yl, thiophen-2-yl, 3-(5-cyano-3,4-dimethylthien-2-yl)-1H-1,2,4-triazol-1-yl, quinolin-3-yl, 1,3-thiazol-2-yl and n is 0 or 1.

10. A compounds selected from:

(11S,21S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(4-(pyridin-3-yl)-imidazol-1-yl)-ethylamino)-methylene]-erythromycin A;

(11S,21S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(quinolin-4-yl)-ethylamino)-methylene]-erythromycin A;

(11S,21S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(4-(pyridin-3-yl)-imidazol-1-yl)-propylamino)-methylene]-erythromycin A;

(11S,21S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(2-(quinoxalin-2-ylsulfanyl)-acetamido)-methylene]-erythromycin A;

(11S, 21S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-((4-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-4-oxo)-butyramido)-methylene]-erythromycin A;

(11S,21S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(4-methoxy-3-nitro-phenyl)-4-oxo-butyramido)-methylene]-erythromycin A;

(11S,21S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(2-hydroxy-4,5-dimethoxy-phenyl)-4-oxo-butyramido)-methylene]-erythromycin A;

5 (11S,21S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(4-oxo-4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl)-4-oxo-butyramido)-methylene]-erythromycin A;

(11S,21S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(4-quinolin-2-yl-1H-pyrazol-1-yl)propylamino)-methylene]-erythromycin A;

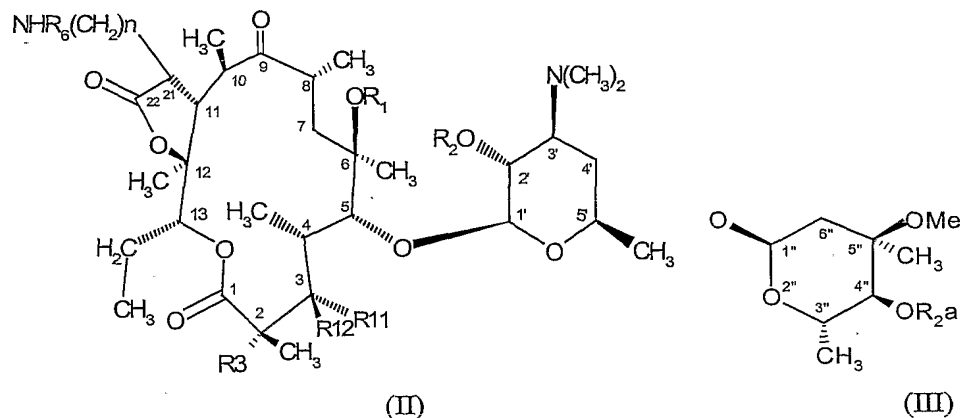
10 (11S,21S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(3,4-dimethoxy-phenyl)-4-oxo-butyramido)-methylene]-erythromycin A;

(11S, 21S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(4-(4-hydroxy-3-methoxy-phenyl)-4-oxo-butyramido)-methylene]-erythromycin A;

(11S, 21S)-3-decladinosyl-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl-(3-(4-(thiophen-2-yl)-imidazol-1-yl)-propylamino)-methylene]-erythromycin A.

15

11. A process for the preparation of a compound of formula (I) which comprises:  
a) reacting a compound of formula (II)



20

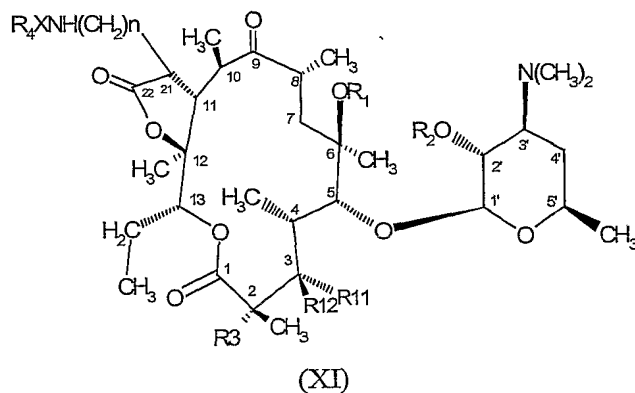
wherein  $R_1$ ,  $R_2$ ,  $R_3$  have the meanings defined in claim 1,  $R_{11}$  is a cladinose derivative of formula (III), in which  $R_{2a}$  is a hydroxy protecting group, or hydroxy,  $R_{12}$  is hydrogen or  $R_{11}$  together  $R_{12}$  is an oxygen atom, with a suitable activated derivative of the acid (IV),  $\text{HOC(O)XR}_4$  (IV) or with a suitable activated derivative of the sulfonic acid (V)  $\text{HOS(O)}_2\text{XR}_4$  (V) respectively wherein  $R_4$  and  $X$  have the meanings defined in claim 1, to produce a compound of formula (I) wherein  $R$  is  $(\text{CH}_2)_n\text{A-X-R}_4$ ,  $A$  is  $-\text{N(R}_6)\text{C(O)-}$  or  $-\text{N(R}_6)\text{S(O)}_2\text{-X}$  and  $n$  have the meanings defined in claim 1;

25

b) reacting a compound of formula (II) with a compound of formula  $\text{R}_4\text{XN(R}_7)\text{C(Y)L}$  (VI), wherein  $L$  is a suitable leaving group,  $R_6$  is phenyl or  $\text{C}_{1-4}$  alkyl,  $R_4$  and  $X$  have the meanings defined in claim 1, to produce a compound of formula (I) wherein  $R$  is  $(\text{CH}_2)_n\text{A-X-R}_4$ ,  $A$  is  $-\text{N(R}_6)\text{C(Y)N(R}_7)\text{-}$  and  $X$  and  $n$  have the meanings defined in claim 1;

30

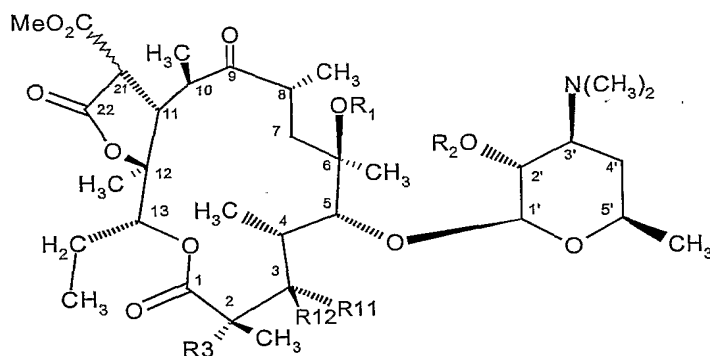
- c) reacting a compound of formula (II) with a compound of formula  $R_4XN=C(Y)$  (VII), wherein  $R_4$  and  $X$  have the meanings defined in claim 1, to produce a compound of formula (I) wherein  $R$  is  $(CH_2)_nA-X-R_4$ ,  $A$  is  $-N(R_6)C(Y)NH-$ ,  $X$  and  $n$  have the meanings defined in claim 1;
- 5 d) reacting a compound of formula (II) with a compound of formula  $R_4XL$  (VIII), wherein  $R_4$  and  $X$  have the meanings defined in claim 1 and  $L$  is suitable leaving group, to produce a compound of formula (I) wherein  $R$  is  $(CH_2)_nA-X-R_4$ ,  $A$  is  $-N(R_6)-$ ,  $X$  and  $n$  have the meanings defined in claim 1;
- e) reacting a compound of formula (II) with a compound of formula  $R_4XOC(O)L$  (IX) wherein  $L$  is a suitable leaving group such as halogen (e.g. chlorine or bromine),  $R_4$  and  $X$  have the meanings defined in claim 1, to produce a compound of formula (I) wherein  $R$  is  $(CH_2)_nA-X-R_4$ ,  $A$  is  $N(R_6)C(O)O$ ,  $X$  and  $n$  have the meanings defined in claim 1;
- 10 f) reacting a compound of formula (II) with a compound of formula  $R_4XCHO$  (X), wherein  $R_4$  and  $X$  have the meanings defined in claim 1, to produce a compound of formula (I) wherein  $R$  is  $(CH_2)_nA-X-R_4$ ,  $A$  is  $N=C(R_6)$ ,  $X$  and  $n$  have the meanings defined in claim 1;
- 15 g) reacting a compound of formula (XI), in which  $R_{11}$  and  $R_{12}$  have the meaning as defined for compounds of formula (II), wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$  and  $X$  have the meanings defined in claim 1, with a compound of formula  $R_6COOH$  (XIa),



20

- to produce a compound of formula (I) wherein  $R$  is  $(CH_2)_nA-X-R_4$ ,  $A$  is  $N=C(R_6)$ ,  $X$  and  $n$  have the meanings defined in claim 1;
- 25 h) decarboxylation of a compound of formula (XII), wherein  $R_1$ ,  $R_2$  and  $R_3$  have the meanings defined in claim 1,  $R_{11}$  and  $R_{12}$  have the meaning as defined for compounds of formula (II),

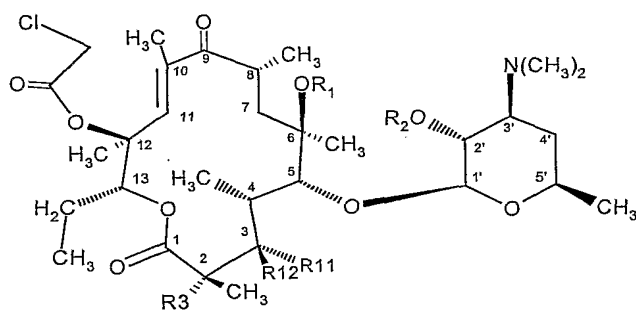
208



(XII)

to produce a compound of formula (I) wherein R is hydrogen;

- 5 i) cyclisation of chlorine derivatives (XIII) wherein  $R_1$ ,  $R_2$  and  $R_3$  have the meanings defined in claim 1,  $R_{11}$  and  $R_{12}$  have the meaning as defined for compounds of formula (II),

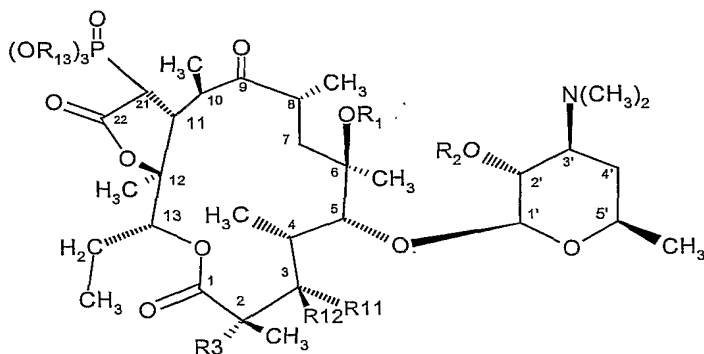


(XIII)

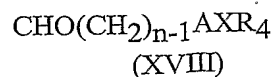
10

to produce a compound of formula (I) wherein R is cyano;

- 1) reacting a compound of formula (XVII), wherein  $R_1$ ,  $R_2$  and  $R_3$  have the meanings defined in claim 1,  $R_{11}$  and  $R_{12}$  have the meaning defined in formula (II) and  $R_{13}$  is  $C_{1-4}$  alkyl, with an aldehyde of formula



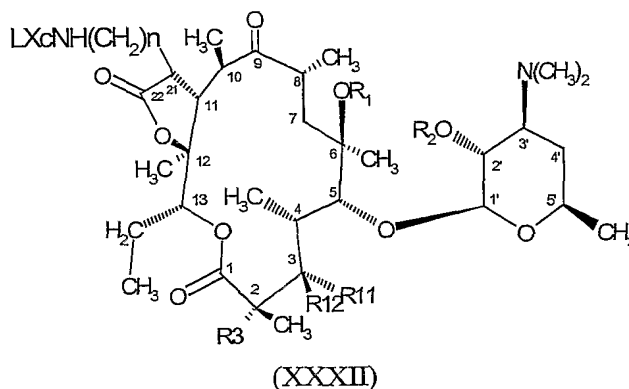
(XVII)



wherein  $R_4$ , X and n have the meanings defined in claim 1, to produce a compound of formula(I) wherein R is  $(CH_2)_nAXR_4$  A and X have the meanings defined in claim 1; and n is an integer from 2 or 3;

m) reacting a compounds of formula (I) in which  $R_1$  has the meanings defined in claim 1,  $R_3$  is hydrogen and  $R_2$  is hydroxy protecting group with a halogenating agent to produce a compound of formula (I) wherein  $R_3$  is halogen;

5 n) cyclisation of a compound of formula (XXXII), wherein L is suitable leaving group such halogen (i.e chlorine or bromine),  $R_1$ ,  $R_2$ ,  $R_3$  have the meanings defined in claim 1,  $R_{11}$  and  $R_{12}$  have the meaning defined in formula (II), X is C<sub>4-5</sub> alkylene chain optionally substituted by one or two groups selected from oxo, 9 or 10 membered fused bicyclic heterocyclic having at least one heteroatom selected from oxygen, sulphur or nitrogen,



15 to produce a compound of formula (I) wherein  $R_1$  is  $(CH_2)_nR_5$ ; and thereafter, if required, subjecting the resulting compound to one or more of the following operations:

i) hydrolysis of the cladinose derivative (III);

ii) conversion of the 3-hydroxy group into the 3-oxo;

20 iii) removal of the protecting group  $R_2$  and

iv) conversion of the resultant compound of formula (I) into a pharmaceutically acceptable salt and solvates thereof.

12. A compound as claimed in any claims 1 to 10 for use in therapy.

25

13. The use of a compound as claimed in any claims 1 to 10 in the preparation of a medicament for use in the therapy of systemic or topical bacterial infections in a human or animal body.

30

14. The use of a compound as claimed in any claims 1 to 10 for use in the treatment or prophylaxis of systemic or topical bacterial infections in a human or animal body.

15. A pharmaceutical composition comprising a compound as claimed in any claims 1 to 10 in admixture with one or more pharmaceutically acceptable carriers or excipients.
- 5 16. A method for the treatment of the human or non human animal body to combat bacterial infection comprising administration of an effective amount of a compound as claimed in in any claims 1 to 10.



## INTERNATIONAL SEARCH REPORT

PCT/GB 01/05665

A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 7 C07H17/08 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	EP 1 114 826 A (PFIZER PROD INC) 11 July 2001 (2001-07-11) cited in the application ----	
A	WO 00 44761 A (MCMILLEN WILLIAM THOMAS ;KANEKO TAKUSHI (US); PFIZER PROD INC (US)) 3 August 2000 (2000-08-03) ----	
A	WO 99 21870 A (SUGIMOTO TOMOHIRO ;ISHII TAKAAKI (JP); MATSURA AKIKO (JP); ASAKA T) 6 May 1999 (1999-05-06) ----	
A	WO 99 21869 A (SUGIMOTO TOMOHIRO ;ISHII TAKAAKI (JP); MATSURA AKIKO (JP); ASAKA T) 6 May 1999 (1999-05-06) ----	
A	FR 2 732 684 A (ROUSSEL UCLAF) 11 October 1996 (1996-10-11) ----- -/--	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

° Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

11 February 2002

Date of mailing of the international search report

22/02/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax: (+31-70) 340-3016

Authorized officer

Bardili, W

## INTERNATIONAL SEARCH REPORT

PCT/GB 01/05665

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 747 467 A (CHANTOT JEAN-FRANÇOIS ET AL) 5 May 1998 (1998-05-05) -----	

# INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/GB 01/05665

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 1114826	A	11-07-2001	BR 0006301 A EP 1114826 A2 JP 2001213895 A	27-11-2001 11-07-2001 07-08-2001
WO 0044761	A	03-08-2000	AU 1675400 A BR 9916969 A EP 1147121 A2 WO 0044761 A2 NO 20013680 A	18-08-2000 06-11-2001 24-10-2001 03-08-2000 19-09-2001
WO 9921870	A	06-05-1999	AU 9649698 A WO 9921870 A1 ZA 9809830 A	17-05-1999 06-05-1999 04-05-1999
WO 9921869	A	06-05-1999	AU 9649598 A WO 9921869 A1 ZA 9809835 A	17-05-1999 06-05-1999 05-05-1999
FR 2732684	A	11-10-1996	FR 2732684 A1	11-10-1996
US 5747467	A	05-05-1998	FR 2742757 A1 EP 0799833 A1 JP 3140703 B2 JP 9176182 A	27-06-1997 08-10-1997 05-03-2001 08-07-1997